

15

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Review: John Hunter on heart disease
W L Proudfit

109

Early results after percutaneous transluminal
coronary angioplasty in 400 patients
*E Sowton, A D Timmis, J C P Crick, B Griffin,
A K Yates, P Deverall*

116

Changes in left ventricular regional asynchrony
after intracoronary thrombolysis in patients with
impending myocardial infarction *D Gibson,
H Mehmel, F Schwarz, K Li, W Kubler*

121

Exercise digital subtraction ventriculography for
the detection of ischaemic wall motion
abnormalities in patients without myocardial
infarction *R Detrano, J Yiannikas,
C Simpfendorfer, R E Hobbs, E E Salcedo*

131

Diagnosis of important fixed coronary stenosis in
patients with variant angina by exercise tests after
treatment with calcium antagonists *H Araki,
N Hayata, T Matsuguchi, A Takeshita,
M Nakamura*

138

Detection of coronary artery disease by thallium
scintigraphy in patients with valvar heart
disease *H V Huikuri, U R Korhonen, J Heikkila,
J T Takkunen*

146

Effects of captopril and a combination of
hydralazine and isosorbide dinitrate on myocardial
sympathetic tone in patients with severe
congestive heart failure *P Daly, J-L Rouleau,
D Cousineau, J H Burgess, K Chatterjee*

152

Reliability of non-invasive estimates of pulmonary
hypertension by pulsed Doppler echocardiography
*M Matsuda, T Sekiguchi, Y Sugishita, K Kuwako,
K Iida, I Ito*

158

Relation between alcohol intake, myocardial
enzyme activity, and myocardial function in dilated
cardiomyopathy: evidence for the concept of
alcohol induced heart muscle disease
*P J Richardson, A D Wodak, L Atkinson,
J B Saunders, D E Jewitt*

165

Computed tomography the investigation of choice
for aortic dissection? *H Singh, E Fitzgerald,
M S T Ruttle*

171

Influence of profuse sweating on systolic time
intervals *M Ishikawa, K Ishikawa*

176

Case reports

Unusual echocardiographic appearance of
intracardiac thrombi in a patient with
endomyocardial fibrosis *M N Wiseman,
M S Giles, A J Camm*

179

Intracoronary thrombolytic treatment: another
hazard *H Singh, M S T Ruttle*

182

Successful balloon aortic valvotomy in a child
with a pulmonary hypertensive duct and aortic
valve stenosis *A F Rickards, J Somerville*

185

Left atrial rupture in osteogenesis imperfecta
M E Rogerson, J D Buchanan, C M Morgans

187

Myocardial infarction in a young man with
systemic lupus erythematosus, deep vein
thrombosis, and antibodies to phospholipid
R A Asherson, I R Mackay, E N Harris

190

Notices

193

Correspondence

194

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British Heart Journal

P. 25. 730

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patches containing a drug
reservoir of 25mg glyceryl
trinitrate (average amount
of glyceryl trinitrate
absorbed per patch in 24
hours is 5mg).
Transiderm-Nitro 10
patches containing
50mg glyceryl trinitrate
(average of 10mg
absorbed per patch in 24
hours).

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attacks of angina pectoris.
**Dosage and
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Transiderm-Nitro 10 patch
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Acute attacks of angina
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hypotension, nausea,
dizziness and allergic skin
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Contra-indications
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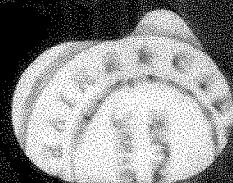
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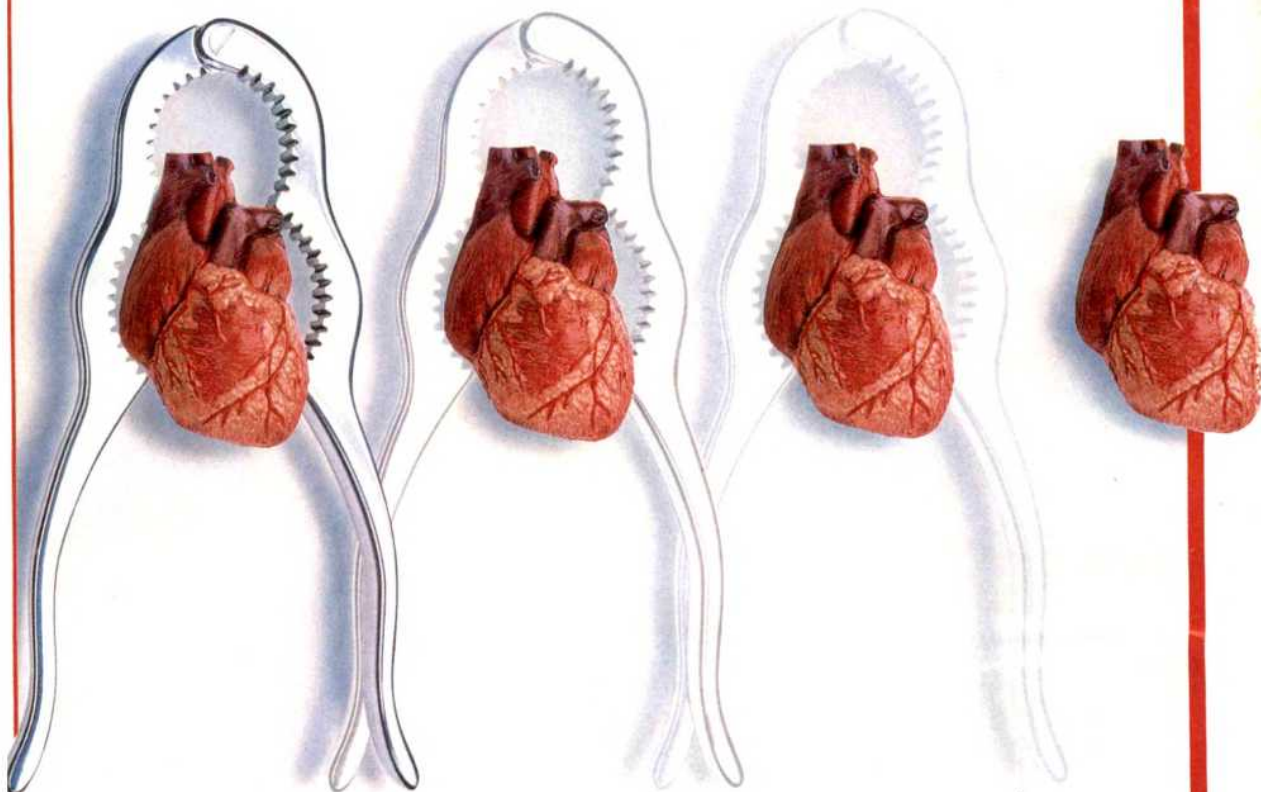
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Review

John Hunter: on heart disease

WILLIAM L PROUDFIT

From the Department of Cardiology, Cleveland Clinic Foundation, Cleveland, Ohio, USA

In August 1777 John Hunter was preparing for a trip from London to Bath in the hope that he might find some relief from angina pectoris. His brother in law, Everard Home, was to maintain his surgical practice and William Bell, a talented artist-surgeon, was a member of the Hunter household.¹⁻³ Hunter instructed these two assistants to prepare a catalogue of his museum of comparative anatomy and pathology during his absence. This was a formidable task because there were hundreds of specimens, many of which were accompanied by scant or no descriptions. By reference to manuscript notes and labels on jars, Home and Bell were able to identify and catalogue much of the material, but many specimens in the pathological section required Hunter's presence for proper organisation and description. More immediate concerns must have demanded Hunter's attention in November after his prolonged absence, and Home's entry into naval service the next year may have prevented attention being paid to the catalogue, but Hunter did not forget it. In the last year of his life (1793) he was about to turn his attention to this important work, after the planned publication of his classic *A Treatise on Blood, Inflammation and Gun-shot Wounds*.² He did not live to see the book published, nor was the catalogue completed. Hunter's distinguished nephew Dr Matthew Baillie and Home were executors of his estate, the principal asset of which was the museum.³ After much effort they were able to persuade parliament to purchase the collection in 1799. It was presented to the Company of Surgeons, soon to become the Royal College of Surgeons. Unfortunately, parliament did not specify that all relevant notes and manuscripts were to be included in the purchase, and they were retained by Home.⁴ William Clift, a 20 year old who had been a resident assistant for 20 months before

Hunter's death, continued to live in the Hunter household until the time of transfer of the museum and he was named as its curator after the move.⁴ During the years between Hunter's death and the sale of the museum, Clift was in extreme poverty because of Anne Hunter's straitened circumstances, but he used part of what little money he could save to buy paper, so that he could transcribe those of Hunter's notes that most interested him. Much later these notes were useful in the completion of a catalogue.⁵

About 30 years after Hunter's death, Sir Everard Home said that he had burned all of Hunter's manuscripts, notes, and letters in accordance with Hunter's orally expressed wish.⁴ Being a great collector and preserver Hunter must have known that the usefulness of an undescribed collection of specimens would be limited, so it seems likely that it was his intention to destroy the original notes and manuscripts. It took Home 30 years to comply with the alleged instructions. Home stated that he spent a great deal of time compiling a catalogue of the museum, but there is no evidence to support his claim. Later, after a series of bitter exchanges with the board of curators of the Hunterian Museum and the board of trustees of the Royal College of Surgeons of England, Home made two presentations of Hunterian manuscripts. Clift soon transcribed many of the medical notes into a series of five bound volumes, recording some of Hunter's experience in the practice of medicine and surgery as well as descriptions of postmortem examinations.⁶ Unfortunately, most of the latter were limited to his experience before 1783, most of the observations of his last decade having been lost or burned. Hunter said that he had done "thousands" of postmortem dissections, of which the recorded material and the museum specimens can only be a fraction.³ Eventually, with the guidance of Clift's compilation, Stanley and Paget were able to assemble a catalogue of the museum in 1848.⁷ Subsequent editions, the last of which was published in 1966 and 1972, have clarified some of the problems in organisation of the

Requests for reprints to Dr William L Proudfit, Department of Cardiology, Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44106, USA.

specimens.⁸ Fortunately most of the pathological material was not damaged by the bombing of the Hunterian Museum in the second world war, although there were other extensive losses.

An additional handicap is that Hunter's notes on postmortem examinations, unlike those of Morgagni, were not intended for publication.⁹ Most are simply anatomical descriptions, with only occasional inductive reasoning. The general arrangement of the Hunterian Museum specimens probably influenced Matthew Baillie in the organisation of his classic, the first modern textbook of pathology, published in the year of Hunter's death.¹⁰ Keele has reviewed the Hunterian Museum specimens of cardiovascular pathology.¹¹

Because the written records of Hunter's many contributions to biology and medicine are incomplete, a review of his knowledge of a restricted area, that is, diseases of the heart, may give a better indication of the depth of his genius. In Hunter's time relatively simple concepts such as congestive heart failure being a specific type of dropsy, the rheumatic origin of much valvar disease, and coronary disease as a cause of angina pectoris had not been published, and clinical examination of the heart was usually confined to checking the pulse. John Hunter was not a bookish scholar, and he was free to make original observations, uninhibited by what "authorities" had stated. Although Volume III of Alexander's translation of Morgagni's great work on pathology was dedicated to "Dr Hunter," and it has been stated that this was John Hunter, it is obvious that John's brother, William, was the physician honoured in the preface.⁹

Congenital heart disease

Congenital malformations of the heart had been occasionally noted but little reported before 1750. William Hunter described three cases in 1783, one of which was what is now called tetralogy of Fallot; however, the description is not complete.¹² In 1781 a 13 year old cyanotic patient of Richard Pulteney died of dysentery.¹³ Necropsy showed an interventricular septal defect and a pulmonary ring that was "much smaller and more firm than is usual." John Hunter mentioned that he had seen this patient—apparently meaning that he was present at the dissection.⁶ Hunter wrote of the "imperfect construction of the heart" saying that "there is a communication between the right and left side, kept up after birth" and that "cases of this kind frequently occur."⁶ To supplement Pulteney's description, Hunter stated that there was dextroposition of the aorta in addition to pulmonary stenosis and interventricular septal defect. Thus Hunter recognised

the essential features of tetralogy of Fallot. Although he indicated that such lesions were commonly encountered, no other cases are recorded in his preserved papers and there are no examples in the museum. When in 1787 Hunter saw a 16 year old girl with cyanosis who was a patient of Caleb H Parry he predicted a poor outcome; he also expressed his wish to know the findings of a post-mortem examination if the prognosis prove to be accurate.³ It is not known whether she died soon afterwards or outlived Hunter.

The other congenital defects that Hunter described were relatively simple. He mentioned canalis arteriosus (ductus arteriosus) and the foramen ovale "... as much open as in the foetus."² It is likely that some of the latter abnormalities were interatrial septal defects. He also studied the structure of the heart in various animals and said that "the foetus of the class possessing four cavities may be classed with the mixed, having but one auricle, by communication between the two and also one ventricle by means of a union of blood although not in the same way (viz ductus arteriosus). The passages are shut up almost immediately after birth, or at least the canalis arteriosus, which immediately prevents the foramen ovale from producing its former effects; therefore it is not so necessary that it should be shut up in the adult."² There is no doubt that Hunter, the evolutionary theorist, recognised the embryological similarity of the human fetal heart to that of lower forms of animal life. He described "transposition of the viscera" without reference to a specific case. Hunter also recognised bicuspid aortic valves and speculated on the congenital origin of the condition in several patients.⁶ One additional case was that of a 14 year old boy who had congenital aortic stenosis, although Hunter did not state the aetiology. Finally, he had one case of two superior vena cavae.

Valvar heart disease

The museum contains 12 specimens of valvar heart disease, but curiously only one with isolated mitral valve disease. Hunter's first resident student, Edward Jenner, however, reported a case of isolated mitral stenosis at the first meeting of the Fleece Medical Society in 1788.¹⁴ There are also 12 descriptions of valvar disease in volumes III and V of Clift's transcriptions of Hunter's notes. Only two of these definitely refer to museum specimens. The notes in volume I:127 and volume III:80 related to specimen P 286, and the description in III:79 is that of specimen P 287. It is evident that Hunter considered isolated aortic valvar disease in the aging adult as being distinct from mixed valvar lesions. He

thought that with advancing years men especially lose elasticity of the aorta and that in diastole the blood "throws" the aortic leaflets shut and, as a result "the valves become thicker and are often very irregular and bony." The result is that "more blood is allowed to regurgitate into the ventricle, than in a regular circulation."² Only in recent years has isolated aortic stenosis in the aging adult been considered to be non-rheumatic.

Hunter did not speculate on the cause of mixed aortic and mitral valvar lesions. Jenner, who often corresponded with Hunter, related valvar disease to the residual effect of rheumatic fever, and talked on this subject at the Fleece Medical Society in 1789, but because his letters to Hunter have not been preserved it is not known whether he communicated this concept to his mentor.¹⁴⁻¹⁶ Dr David Pitcairn, a friend and one of Hunter's personal physicians, has been credited with proposing the same aetiological hypothesis as Jenner at about the same time, but Pitcairn was not a medical writer. The claim for Pitcairn rests on a footnote in the second edition of Baillie's textbook of pathology.¹⁷ It appears that Baillie was discussing cardiac enlargement rather than valvar disease specifically. It is possible that Pitcairn was more restrictive in his speculation, and he may have mentioned this belief to Hunter, but this is not known.

Pericarditis

Eight of the museum specimens show pericardial disease and four postmortem descriptions are given in Cliff's transcriptions. Several cases were probably localised pericardial adhesions, and several were examples of acute pericarditis. One specimen in the museum is the "heart of a man who had died of a fever and violent pain and oppression of his breast. The whole heart is covered with gluten, from inflammation which made the pericardium adhere." A woman had a large bloody pericardial effusion with active disease of the visceral pericardium. Hunter said that "the heart and pericardium looked as if they had been torn by cats."¹⁶ A third case, a young man, died of a fever and was found to have a bloody pericardial effusion as well as non-sanguineous ascites. A young woman had pericardial effusion associated with tubercles of the lung. The Earl of Bristol, although he had no apparent cardiac symptoms and his death was not cardiac in cause, had a small heart with a diffusely adherent pericardium.

Endocarditis

The only definitely dated cardiac case dissected by Hunter after 1783 is that of a six and a half year old

boy who died in 1793, the year of Hunter's own death. He had palpitation from the age of three years and an apical thrill had been noted. A fever was followed by coma and death. Hunter found the mitral and aortic valves to be "shriveled and thickened" as well as calcified, and the aortic valve was bicuspid. The chordae tendinae "had a number of small bodies like granulations growing on them."¹⁶ Death was caused by a cerebral haemorrhage. Bacterial endocarditis seems to have been the terminal illness; however, the bacterial origin of some infectious diseases was not recognised in Hunter's day. A museum specimen shows active endocarditis involving the mitral and aortic valves with ruptured chordae, and another specimen shows calcific aortic stenosis with a small active vegetation in one cusp. In another specimen numerous small bodies were found to be adhering to prominent fasciculi but the description does not strongly suggest endocarditis.

Cardiac enlargement

In nine cases in Hunter's casebook an increased heart size was the most impressive finding. In one (a 13 year old girl) other gross findings may have been omitted inadvertently. In two cases there had been irregularity of the heart for several years before death. In one other patient the pericardium was "furred over with some coagulable lymph." This may have represented uraemic pericarditis. Hunter mentioned pallor of the myocardium in one case ("like the flesh of veal"). The remaining four cases occurred in men who had no abnormality described except for enlargement—in two instances Hunter stated that the heart appeared "sound" except for the size.⁶ He said that "we see every day enlarged hearts... and yet no visible mechanical cause existed."² Probably these were examples of cardiomyopathy or hypertensive heart disease, but indirect blood pressure could not be measured for another century.

Arrhythmias

In addition to the two necropsy cases mentioned above, Hunter reported one patient with an arrhythmia whom he had seen both clinically and at necropsy. He described attacks of paroxysmal tachycardia with a rate of 160 beats per minute. Attacks could last "for weeks" but might "leave him all at once." An apical scar was found at necropsy. The coronary arteries were not mentioned. He seems to have examined a 13 year old girl both clinically and at necropsy. She had palpitation since infancy; the heart rate was "inconceivably rapid." She developed congestive heart failure and died, and dissection showed appreciable cardiac enlargement, but the

heart was not otherwise described. Two 16 year old girls were seen clinically and mentioned in Clift's transcriptions. In one the heart rate was 192–216 beats per minute during attacks. The other girl probably had valvar disease; she had an apical thrill and her carotid artery pulsed visibly. The noise of her heart during paroxysms was audible to others. The left radial pulse was absent and the arm was weak and "black" during attacks. Another remarkable case was that of General Robertson who had a heart rate of "not thirty-six in the Hour."⁶ He was dropsical, jaundiced, and asthmatic. Hunter said that "his pulse was not quite 3 strokes in five minutes; it was not more than 8 strokes in a quarter of an hour."

Cardiac function

Hunter recognised that the heart could be diseased without having an adverse effect on general health. He thought that "the heart may be in some degree disordered in its action; is therefore to be considered as a local agent very little affecting the constitution sympathetically, except by means of failure in its duty."² He seems to have confused angina pectoris and dyspnoea due to congestive heart failure at least in some instances.^{2,6} He believed that "when the heart ceases to act, or cannot get rid of its blood... respiration ceases, or is performed so imperfectly as to have nearly the same effect... In such inspirations I conceive that so little air is taken in as hardly to reach the cells of the lung, so as to be able to influence blood circulating to those cells."² Two observations may have impressed on Hunter the importance of apnoea. He was apnoeic during an episode of severe coronary pain or at least he had to force himself to breathe.² Also he had observed at least two patients who had Cheyne-Stokes respiration, which he may have attributed to heart disease.⁶

Hunter had a rational concept of left ventricular ejection. He stated that in the relaxed state at necropsy the left ventricular volume was about four ounces. In life under normal conditions he thought that the diastolic volume might be three ounces, of which two ounces might be expelled during systole. He believed that increased cardiac output could result from increase in the heart rate or from augmentation of contractility. Increased diastolic filling was not mentioned. When the left ventricle was diseased Hunter speculated that increased cardiac output could result only from increased heart rate.

Ischaemic heart disease

Early in the spring of 1772, a 51 year old man read a summary of William Heberden's published description of angina pectoris in the literary magazine *Crit-*

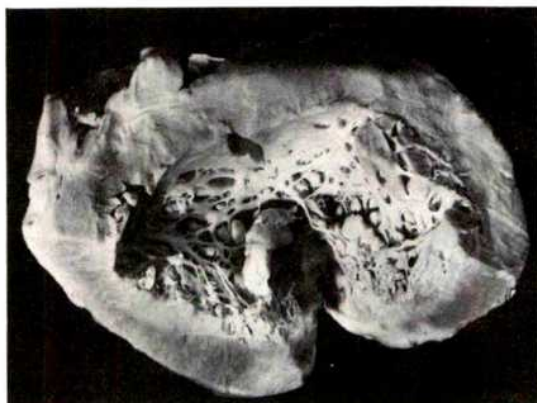


Fig 1 Thinning and scarring of the incised apex of the left ventricle and an endocardial thrombus, as well as many postmortem thrombi (specimen P 150, Hunterian Museum, Royal College of Surgeons of England).

ical Review.^{18,19} He recognised the similarity to his own symptoms and wrote to Heberden that "I have never troubled myself much about the cause of it, but attributed it to an obstruction of the circulation, or a species of rheumatism." Believing that sudden death was likely, he left instructions that Dr Heberden be notified "if it please God to take me away suddenly" and gave permission for "an examination of my body, as will show the cause of it." His premonition was fulfilled less than three weeks later and Heberden engaged the "experienced and accurate anatomist, Mr J Hunter, to open the body." Nothing was found to account for angina; Heberden concluded that angina was not due to an organic disease.¹⁹ Edward Jenner attended this necropsy, performed near the end of Jenner's two year residence with Hunter, and the negative findings must have bothered him. Years later, after he had ascribed angina pectoris to coronary artery obstruction, he wrote that he was "almost certain that the coronary arteries were not examined" in the case of Heberden's correspondent.²⁰ No record of the dissection has been found among Hunter's preserved manuscripts. Heberden gave a report of this case to the College of Physicians in November 1772 and also presented correspondence from Dr John Wall, the Worcester physician, indicating that aortic stenosis was responsible for angina pectoris in a patient in whom necropsy was performed. Most of Wall's patients with angina had died suddenly.²¹ These communications were not published until 1785.

John Hunter's records show that he performed necropsies on at least three cases of ischaemic heart disease before that of Heberden's correspondent, and many of his notes are not dated. Two of the

three cases had ventricular aneurysms and the third had an apical scar and an endocardial thrombus (fig 1). The circumstances of death were not described in a man who had experienced paroxysmal tachycardia, one man died suddenly, and the third man had experienced a stroke (ventricular thrombus and possible cerebral embolus). In the latter case (in 1770) Hunter reported that "when I cut into the right ventricle I found the coronary artery as it goes between the auricle and ventricle, ossified."⁶ He made no comment on the coronary disease, and whether he correlated it with the clinical presentation is not known.

On 13 March 1775, Mr Rook, a 54 year old man who had angina pectoris, died suddenly "in a sudden and violent transport of anger." His physician, the eminent John Fothergill, suspected that angina pectoris was due to disease of the heart, and he asked John Hunter to "open" the body.²² Hunter found calcific aortic stenosis and mitral valvar disease and that two coronary arteries "from their origin to many of their ramifications upon the heart, were become one piece of bone." The degree of arterial narrowing was not stated. Although Hunter's notes



Fig 2 Dilated fibrotic left ventricle in coronary artery disease (specimen P 1150). The emphysematous changes in the myocardium occurred after death. The coronary lesions described in the text are not shown.

indicate that Mr Rook had "felt frequent pain in the arms" still "there was nothing very remarkable in his case worth taking notice of."⁶ Perhaps Heberden and Fothergill had not yet impressed Hunter with the symptoms and importance of angina pectoris. This was at least the second case of "ossification" of the coronary arteries encountered by Hunter.

A specimen (P 1150) in the Hunterian Museum shows a thrombus in a thickened anterior descending artery. The date of death of the patient is unknown, no clinical description was given, and the specimen does not correspond to any preserved description in Hunter's postmortem observations. This specimen is attributed to Hunter in the latest catalogue, which states that the thrombus probably occurred postmortem.⁸ If the heart was in the original collection, Hunter must have believed that the thrombus was important. The specimen also shows ischaemic cardiomyopathy (fig 2). Another undated record refers to the findings in the case of Mr Almack who is said to have had "gout" in the extremities and stomach and died of a stroke. Non-articular "gout" was a common diagnosis at the time. At necropsy the "heart was extremely flaccid and flabby; and, as it were, half putrid." It is possible that Mr Almack had acute myocardial infarction with cerebral embolisation.

It is curious that evidence of ischaemic heart disease was not recorded in any case after 1775 except for that of Mr Coxwell, whose notes are undated, but it is probable that he died in 1782 or later.²³ This man had angina pectoris associated with calcific aortic stenosis, but the coronary arteries were not mentioned. As noted previously, Hunter's records contained little information on necropsies performed after 1783 although he remained an active pathologist.

Hunter's symptoms of coronary disease started in 1773 with an attack of severe epigastric pain accompanied by pallor "...the appearance of a dead man."² The maximal pain lasted for 45 minutes and he was "perfectly recovered in two hours." Subsequently he did well, but in the spring of 1777 he had severe vertigo, from which he recovered slowly, and angina pectoris became a problem at this time. He was advised to go to Bath for spa therapy and, while there, Jenner diagnosed angina pectoris.¹⁶ Improvement was slow and he continued to have angina for the remainder of his life.² In 1785 he had another prolonged episode of pain and exertional angina was accentuated. He visited the spa at Tunbridge Wells for two weeks and Bath for one month. Jenner was concerned about Hunter's condition when he saw him in Bath in 1785, and Jenner's friend, Caleb H Parry, a Bath physician, gave Hunter sound medical advice.²⁰ The following

spring, Jenner recognised the relation between angina pectoris and coronary disease, but did not inform Hunter because he did not want to disturb his friend.²⁰ Hunter's biographers point out that he was aware of the possibility of sudden death and undoubtedly he associated angina pectoris with disease of the heart.^{1 3 24-26} From his necropsy experience, he may have related angina to aortic stenosis and even speculated on the role played by "ossified" coronary arteries, although there is no evidence to support such a speculation. Hunter's angina was severe in 1789 and probably for the next four years of his life. He had nocturnal pains as well as exertional discomfort. Hunter died suddenly on 16 October 1793 and necropsy confirmed Jenner's prediction that coronary artery disease would be found.^{2 20} Hunter's wish that his heart should be preserved was not honoured.⁴

Although many of Hunter's manuscripts are lost, and few inferences are recorded in his descriptions of postmortems, it is clear that he had remarkably advanced insights into the nature of heart disease. Some of his observations were published by his nephew Matthew Baillie in his epochal textbook of morbid anatomy. Baillie also used anatomical drawings of William Bell and William Clift, both protégés of Hunter. Hunter influenced the thinking of Jenner and Parry in a way that led them to propose and develop the ischaemic theory of angina pectoris. He was instrumental in introducing a new era in British medicine. John Hunter left a message for us: trust careful personal observations rather than authoritative opinion, if there is a conflict.

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Early results after percutaneous transluminal coronary angioplasty in 400 patients

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SUMMARY In a consecutive series of 400 patients treated by percutaneous transluminal coronary angioplasty 212 had single vessel disease, 142 had multivessel disease with only one vessel dilated, and 46 had multivessel dilatation. In addition sequential stenoses were dilated in the same vessel in all groups. There was no mortality among patients with single vessel disease. Success rates varied from 83% to 90% according to the artery in which angioplasty was attempted. Urgent surgery was required by 3.8%. Primary success was lower (74%) in the presence of multivessel disease and complications were more frequent, with four deaths (2.8%). In 46 patients with multivessel disease in whom all important lesions were dilated during the same procedure the overall primary success rate was 76% and within the last year of the study it was 91%. One (2%) patient died and three (7%) required urgent surgery. Twelve (86%) out of 14 stenosed vein grafts were successfully dilated and eight (53%) chronically occluded vessels were re-opened; in both groups there were no deaths, no infarctions, and no need for urgent surgery. In all groups symptoms improved greatly and predischARGE exercise tests showed that there was no reversible ischaemia in 94% of patients with single vessel disease or in 65% of patients with incomplete revascularisation. Six months after the procedure 95% of the patients had improved symptomatically and 80% had normal exercise tests after one year.

Percutaneous transluminal coronary angioplasty is the method of choice in single vessel disease and its use also results in a high proportion of other patients becoming symptom free. Complication rates are low and for selected patients results that are equivalent to those of cardiac surgery are obtained.

Since the first report of coronary angioplasty in a patient by Gruentzig *et al* in September 1977¹ the procedure has been increasingly used. In 1984 40 000 patients were treated in this way in the United States.² We estimate that during the same year only about 500 patients were treated by coronary angioplasty in the United Kingdom. We present our results after the first angioplasty procedure in a consecutive series of 400 patients treated over the past five years. Three per cent of the patients we describe were treated up until the end of 1981 and a further 12% were treated during 1982. The remaining 85% were treated in the subsequent

2½ years, indicating the same rapid increase in the use of this technique as has been reported in other countries.

Patients and methods

This series includes 342 men (mean age 52.3 years, range 29-76) and 58 women (mean age 53.2 years, range 32-75). All gave a history of angina, which in 73% was provoked by minimal exertion or occurred at rest (grades 3 and 4). One hundred and fifty nine (39%) patients had previous myocardial infarction. This was anterior in 84 (21%) of the series, inferior in 64 (16%), and multiple in 11 (3%). Thirty two (8%) had undergone previous graft operation, 52 (13%) presented as emergency cases of uncontrolled angina despite full medical treatment in hospital, 12 (3%) were treated after intravenous streptokinase

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had been given early in the development of myocardial infarction, and four (1%) underwent the procedure during the early stages of infarction in an attempt to reverse the process.

ANGIOPLASTY

Angioplasty was carried out according to methods originally described by Gruentzig *et al*³ and subsequently modified throughout the series as new techniques and new equipment were introduced.^{4,5} Initially, non-steerable balloons were used but steerable guide wires were subsequently used to cross the stenosis and these were followed by the balloon catheter. Apparatus produced by several different manufacturers was used, particularly Schneider (Zurich), Advanced Cardiovascular Systems (USA), American Hospital Supplies, Meditech (USA), and SciMed (USA). Both brachial and femoral arteries were used with the choice of access depending upon whether the vessel had been recently catheterised, in which case it was not used for the angioplasty approach. A history of intermittent claudication was regarded as a relative contraindication to the femoral route. The procedure was carried out via the brachial approach in 102 (men 91, women 11) and from the leg in 298 (men 251, women 47). The results did not differ and the figures have been combined in this paper. The degree of stenosis was judged by more than one observer as the obstruction in luminal diameter, taking account of all available views and not only the view showing the greatest obstruction. If an artery filled antegradely but no visible connection could be seen between proximal and distal portions (that is, it was "disconnected") the stenosis was classified as 98%. An artery was classified as being occluded if there was no antegrade filling.

All patients were pretreated with 10 mg nifedipine liquid sublingually and were given both sublingual and intracoronary nifedipine or isosorbide dinitrate or both in the event of spasm. In all cases the contrast medium was Omnipaque 350 (Nyegaard) and frequent injections of half strength medium were given proximally and distally to confirm the position of the wire and balloon. The balloon was inflated for 30–60 s and occasionally longer at pressures of 5–10 atm (505–1010 kN/m²). Inflations were repeated until dye injections showed wide dilatation of the stenosis and any gradient had been effectively eliminated. After removal of the guide wire and the balloon, full strength contrast was injected to visualise the artery before the introducer was removed. Transstenotic gradients were measured before and after each inflation whenever possible (81% of procedures). Some makes of catheter could not be used to measure gradients. There was no significant

difference in the frequency with which gradient could be successfully measured in different vessels.

At the start of the procedure patients were given 10 000 units of heparin intra-arterially. They were also given 1000 units of heparin/h intravenously for 24 hours after the procedure. In addition, an intravenous infusion of isosorbide dinitrate (usually 5 mg/hour) was maintained for 24 hours. This dose was reduced if the blood pressure fell and was increased if chest pain or ST segment changes appeared. The patients were then mobilised and treated with oral isosorbide and nifedipine for the first six weeks and with soluble aspirin 300 mg daily for the first year.

In successful cases we used a treadmill exercise test with the Sheffield modification of the Bruce protocol⁶ on the third day after the procedure and before the patient's discharge from hospital. Exercise testing was repeated after six months and then every year.

The initial dilatation was classified as a primary success if (a) the lesion was crossed with a balloon and dilated to leave $\leq 50\%$ obstruction of the transluminal diameter that was compared with the adjacent normal vessel; (b) the transstenotic gradient, where measurable, was reduced to 10 mm Hg or less; and (c) there was no serious complication (patient death, artery occlusion, referral for urgent surgery). These three criteria are considerably more stringent than that of a simple reduction in degree of stenosis by 20% which is often used to define success. Various definitions of stenosis have been assessed in Rotterdam and the presence or absence of a 50% luminal diameter stenosis has been shown to be the most satisfactory angiographic criterion and has been adopted by most centres.⁷

Where more than one lesion was present in the same artery the result for that artery was classified as a success only if all the stenoses were successfully dilated. When more than one artery was attempted the procedure was classified as a success only if all stenoses in all the arteries attempted were successfully removed at the same procedure.

Results

SINGLE VESSEL DISEASE

Two hundred and twelve patients (mean age 51.5, range 29 to 76 for men and 51.4, range 32 to 76 for women) had disease in only one vessel. There was a total of 248 stenoses (1.2 stenoses/patient) and all were attempted. Two hundred and seven stenoses in 172 vessels were successfully dilated, giving primary success rates of 83% for stenoses and 81% for both arteries and patients.

If only non-occluded vessels are considered then

the primary success rate was 86% for the left anterior descending, 90% for the circumflex, and 88% for the right coronary artery.

In vessels where the stenosis was successfully dilated the mean obstruction was 89% and this was reduced to 8% after a mean of 6.4 dilatations. The transstenotic gradient could be measured in 165 patients and had a mean value of 60 mm Hg. This was reduced to 2.1 mm Hg after angioplasty.

There were no deaths related to the procedure. Eight (3.8%) patients were referred for urgent surgery and nine (4.3%) patients had electrocardiogram changes confirming myocardial infarction. Of these six had non-specific creatine kinase enzyme activities exceeding 1000 units/l (laboratory activity to 220 units/l). An additional six patients had slightly raised creatine kinase activities (mean 300 units/l). This was not associated with any cardiac incident or electrocardiogram change and we attribute it to local changes at the site of catheterisation.

MULTIVESSEL DISEASE—ONE VESSEL DILATED

There were 142 patients in this group (mean age 52.3, range 31–75 for men and mean age 51.2 years, range 35–66 for women). The total number of diseased arteries was 374 and the total number of stenoses was 401, giving an average of 2.6 diseased vessels and 2.8 stenoses/patient.

The primary success rate was appreciably lower for stenoses (74%) and for both arteries and patients (68%). The complication rate in this group was also higher than in those with single vessel disease and there were four (2.8%) procedure related deaths. Twelve (8.4%) patients were referred for urgent surgery and 10 (6.5%) patients had myocardial infarction, with two of the deaths occurring in these patients.

MULTIVESSEL DILATATION

Forty six patients had more than one vessel dilated at the same procedure and this group was made up of 38 men (mean age 53.4 years, range 36–74) and eight women (mean age 53.8, range 40–66). Twenty had previous infarction—anterior in 10, inferior in nine, and both inferior and anterior in one of the patients. Forty one patients had two vessels dilated and five had three vessels dilated. A total of 110 stenoses in 95 arteries were attempted, giving overall rates of 2.4 stenoses and 2.1 arteries per patient attempted. Eighty four of the stenoses were dilated (primary success rate of 76%) and all lesions were dilated in 69 (73%) of the 95 arteries. One (2%) patient died, six (13%) developed myocardial infarction, and three (6.5%) were referred for urgent surgery. It seems likely that operator experience is a major fac-

tor in treatment of multiple lesions and our current results show primary success rates of 91% for stenoses and 88% for arteries over the last year.

GRAFTS

Stenosed vein grafts were attempted in 14 patients (12 men and two women). In 12 (86%) cases the lesion was successfully removed with the stenosis being reduced from a mean of 82% to 7%. There were no deaths, no patients suffered myocardial infarction, and there were no referrals for urgent surgery.

OCCLUDED VESSELS

Attempts were made to reopen chronically occluded vessels (blocked more than three months) on 15 occasions and were successful in eight (53%). There were no deaths, no myocardial infarction, and no referrals for urgent surgery.

LEFT MAIN STEM DISEASE

This was present in seven (1.8%) of the patients and dilatation was performed in three. One of these had a patent graft to the circumflex artery, one had a stenosed graft to the left anterior descending artery which was also dilated at the same procedure, and one had no grafts. The mean stenosis in these three arteries was 80%, and the final value was 13% after a mean of nine dilatations. One additional patient had occlusion of the left main stem, left anterior descending, circumflex, and right coronary arteries with an 85% stenosis in a graft to the right coronary artery. This graft was dilated but an attempt to reopen the occluded left main stem was unsuccessful. There were no deaths, no patient had an infarction, and there were no referrals for urgent surgery.

LESIONS NOT DILATED

A total of 523 stenoses were attempted in the 400 patients and 412 (79%) of these were successfully dilated. The table shows the degree of stenosis in the major vessels in successful and unsuccessful attempts.

Table Results of percutaneous transluminal angioplasty

	LAD (%)	Cx/OM (%)	RCA (%)
Success:			
Initial stenosis	90	87	85
Range	58–98	60–98	60–98
Final stenosis	11	11	14
Failure:			
Initial stenosis	94	82	89
Range	80–98	60–98	75–98

LAD, left anterior descending coronary artery; Cx/OM, circumflex obtuse marginal coronary artery; RCA, right coronary artery.

There is no significant difference in the degree of stenosis and we attribute these failures to the position of the stenosis in the arterial tree, to the anatomical structure including the presence of calcification, and to operator inexperience. Many of these stenoses were crossed with a guide wire but we were unable to follow this with the balloon because the guiding catheter was displaced.

EXERCISE TESTING

Predischarge exercise tests were performed by all patients who had one or more lesions successfully dilated, who did not suffer myocardial infarction, and who were not referred for urgent surgery. In patients with single vessel disease the results of 94% of the tests were completely normal but where additional vessels were diseased only 65% had normal tests. Of the patients followed for at least one year 80% had completely normal exercise tests at that point.

EFFECT ON ANGINA

The severity of symptoms was graded from 1 (angina on vigorous exertion only) to 4 (angina at rest or on trivial movements) and the symptoms that were present before percutaneous transluminal coronary angioplasty were compared with those one month after angioplasty. Fifty three (13%) patients had improved by four grades and another 42% had improved by two or three grades. The results at six months considered on an "intention to treat" basis show that 95% of the patients had improved. When the patients who were treated surgically either initially or within this six months follow up period because of relapse are excluded the improvement rate is 97%.

CLINICAL RELAPSE

Patients were classified as having relapsed if any of the following criteria were met: (a) recurrence of any degree of angina in a patient who had previously been symptom free; (b) deterioration by two grades in the level of angina in patients who had not become symptom free; (c) appearance of ischaemic changes on exercise testing in a patient who previously had a normal test.

Fifty four patients developed one of these criteria within the first six months—a clinical relapse rate of 14%. All these patients are being restudied by angiography, and in many cases treatment by further percutaneous transluminal coronary angioplasty has already been possible. Full details of the relation between results of exercise testing, symptoms, relapse, and angiographic findings over the five year period will be reported elsewhere.

Discussion

Results for primary success in percutaneous transluminal coronary angioplasty have varied over the past few years with relatively low figures for operators in the early stages of the learning curve. The National Heart, Lung, and Blood Institute Registry reported a success rate of 67% in 1981 and recently a rate of 52% has been reported elsewhere for patients with stable angina.⁸ In both studies success was established by an increase in the luminal diameter of $\geq 20\%$.⁹ With improved operator experience and the introduction of new techniques figures of 80% to 90% or higher are currently being reported from many centres¹⁰ and this is in keeping with our own figures for patients with single vessel disease. The situation is confused by the use of several different definitions of success and it no longer seems reasonable to include patients in whom a 90% lesion was reduced to a 70% stenosis. Our initial experience of a lower primary success rate in the presence of multivessel disease has been reported elsewhere^{11,12} although it is not universal and Hartzler's group recently reported 92% success in primary dilatation in patients with multivessel disease.¹³ Our current figure is 91%.

The National Heart, Lung, and Blood Institute Registry has reported that primary success is lower in women¹⁴ but our own data show that in single vessel disease 83% of the stenoses attempted were successfully dilated in both women and men; these included multiple stenoses in the same artery. Despite the inability to measure gradients with some of the dilatation equipment available and occasional technical problems caused by damping from the guide wire, we consider elimination of a gradient to be valuable confirmatory evidence that a stenosis has been successfully relieved. This view is supported by others,² and a report on a large group of patients from Emory University has shown that a final transstenotic pressure gradient of ≤ 15 mm Hg was associated with a low restenosis rate.¹⁵ The current range of dilatation equipment again allows recording of transstenotic gradients.

The attempted disobliteration of totally occluded arteries is a relatively recent development and the long term results cannot yet be adequately assessed. Our early findings of 53% primary success, however, resemble those (57%) in 49 patients presented by Serruys *et al*¹⁶ and in 76 patients reported by Kereiakes *et al* (53%).¹⁷ Success rates for acute occlusions are likely to be considerably higher.

The aim of percutaneous transluminal coronary angioplasty and of coronary artery bypass grafting is total revascularisation, but considerable relief can be obtained by dilatation of one vessel in patients with

multivessel disease and this finding is now being widely reported.¹⁸ When revascularisation is incomplete it is not surprising that maximum tolerance exercise tests produce ischaemic changes even if the patient is symptom free in ordinary life, and it is not yet clear whether minor lesions should be attempted. We did not attempt to dilate stenoses of $\leq 50\%$ obstruction (table). A follow up study in patients where lesions of $\leq 60\%$ stenosis were dilated showed that restenosis was often more severe and that the disease process may even be accelerated¹⁹ and so at present it seems reasonable to attempt dilatation only in lesions producing obstruction of 50%.

The problem of early reocclusion after an apparently successful angioplasty is well recognised.²⁰ The cause of these early stenoses is largely unknown, although early intimal hyperplasia, medial dissection, and new fibrous plaques have all been suggested as likely explanations.²¹ Our symptomatic relapse rate of 14% in six months does not include those patients with recurrent lesions that can only be diagnosed by angiography. As a result the figure is lower than that found in series followed up by routine angiography.

In patients with one vessel disease the complication rate has been remarkably low with no mortality and only a 4% myocardial infarction rate; 85% of the patients were completely free of angina at four weeks, and this early symptomatic benefit is well sustained beyond six months. Provided long term results remain satisfactory it appears that percutaneous transluminal coronary angioplasty for single vessel disease is the treatment of choice and can be carried out with a very low complication rate and a high chance of success.

The implications for the future depend mainly on the outcome of multivessel or multilesion procedures. It is already becoming clear that revascularisation so that no major vessel is left with a stenosis of $> 50\%$ is an important factor in preventing recurrent symptoms and provided this can be achieved it is suggested that patients with multivessel disease may achieve results similar to those with single vessel disease.²² Despite the lack of complete revascularisation in multivessel disease in which only one vessel was dilated, 59% of the patients obtained complete relief of angina and most became symptom free in ordinary life. Only 8% of these patients with multivessel disease continued to suffer severe symptoms (angina grades 3 or 4) four weeks after angioplasty. The application of the technique to patients with unstable angina or even with early infarction enlarges the indications for angioplasty as does the demonstration that completely occluded vessels can often be reopened.

This method of treatment has immediate economic benefits to the patient who can leave hospital within a few days and does not need a lengthy convalescent period. Although restenosis remains a problem, further angioplasty is almost always possible and frequently achieves better results than the initial procedure, unlike repeat coronary artery bypass grafting which carries a higher risk of complications and mortality²³ and can only be repeated once or twice.

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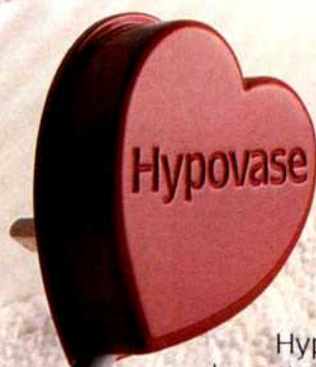
PRESCRIBING NOTES

Use Control of mild to moderate hypertension. 'Inderal' LA and Half-'Inderal' LA are also indicated for angina, anxiety, essential tremor, thyrotoxicosis and prophylaxis of migraine. **Dosage and administration** **Hypertension** One capsule daily of 'Inderex' or one capsule daily of 'Inderal' LA increasing by increments of one capsule of Half-'Inderal' LA if required. **Other indications** One capsule daily of Half-'Inderal' LA increasing to the equivalent of 3 capsules daily if required. **Elderly patients** Start with one capsule daily Half-'Inderal' LA. **Contraindications** Heart block; bronchospasm; after prolonged fasting; and in metabolic acidosis. Addition-

thiazides. **Precautions** Untreated cardiac failure; bradycardia. Treatment modifies tachycardia of hypoglycaemia. Transference from, or discontinuance of, clonidine. Prescription of Class I antidysrhythmic agents. Co-administration with verapamil. Anaesthesia. Pregnancy. Cessation of beta-blocker therapy should be gradual in patients with ischaemic heart disease. Additionally with 'Inderex'; diabetes; hepatic cirrhosis with ascites; and co-administration of digitalis or lithium containing preparations. **Side effects** Cold extremities, nausea, insomnia, lassitude and diarrhoea are usually transient. Isolated cases of paraesthesia of the hands. Rashes and

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Changes in left ventricular regional asynchrony after intracoronary thrombolysis in patients with impending myocardial infarction

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SUMMARY Ventriculograms obtained before and a mean (SD) of 4.3 (2.5) weeks after intracoronary thrombolysis in 23 patients who were treated within 3.5 (3.1) hours of the onset of pain were examined for changes in asynchronous left ventricular wall motion. Lysis was achieved in 19 patients, and in 16 the affected artery was still patent at restudy. Angiograms were digitised frame by frame. Left ventricular volumes, ejection fraction, and peak ejection rate were all unchanged after thrombolysis, whereas peak filling rate fell, whether or not patency was achieved or maintained. Regional wall motion was examined by means of isometric and contour plots. The area supplied by the affected coronary artery showed simple hypokinesis or akinesis in 10 cases, which was unchanged at the second study in nine and improved in one. The commonest manifestation of asynchrony was delayed inward motion during isovolumic relaxation. This was present in 12 cases with or without associated hypokinesis; after thrombolysis wall motion improved significantly in eight and returned to normal in six, significantly more frequently than it did in patients with simple hypokinesis. Dyskinesis (three patients) and hyperkinesis (five patients) resolved in all. Outward wall motion during isovolumic relaxation reverted to normal in four out of five cases, and outward motion during isovolumic contraction reverted to normal in five out of seven. The frequency of improvement was also increased when the circulation to the affected segment was not compromised by an important residual stenosis. Flow in the affected artery was re-established or maintained significantly less frequently when simple hypokinesis or akinesis was present at the first study. These observations provide further evidence that asynchronous wall motion early after acute myocardial infarction represents residual contractile activity, and suggest that knowledge of its presence and distribution may be useful in assessing patients on whom thrombolysis is performed.

Thrombolysis and other procedures for acute revascularisation can prevent the development of infarction after coronary artery thrombosis in the absence of adequate collateral flow.^{1,2} During this early period after the onset of symptoms abnormal timing of wall motion is more common than a simple reduction in amplitude.³ Asynchronous movement

would be expected when the contractile activity of affected myocardium is reduced but not wholly lost. The present investigation was designed to follow the fate of myocardial segments that showed such asynchrony after thrombolysis had been performed, and to compare it with that of the more commonly studied hypokinesis. If asynchrony is indeed the result of a lesser degree of ischaemic injury than that which causes simple hypokinesis, the effects of re-establishing flow might be correspondingly greater. Asynergy might thus be a useful marker for the physiological consequences of thrombolysis in individual patients.

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Patients and methods

Twenty three patients who fulfilled the criteria for intracoronary thrombolysis were studied by left ventriculography and coronary arteriography at the University Hospital, Heidelberg⁴ within 3.5 (1.3) hours (mean (SD)) of the onset of pain. Other data from these patients have been included in earlier studies.⁴⁻⁶ The patients were premedicated with heparin (7500 units intra-arterially) and prednisone (250 mg intravenously). Intracoronary glyceryl trinitrate (0.2-0.4 mg) was administered, and then intracoronary streptokinase (2000 units/min) was given until the patency of the artery was re-established or until a total dose of 200 000 units had been given. Coronary arteriography was repeated every 15 minutes throughout the procedure. The patients were then electively restudied 4.3 (2.5) weeks later. Left ventriculography was performed in the 30° right anterior oblique projection with an injection of 40 ml Urografin at a flow rate of 12 ml/s through a pigtail catheter. The cine film was exposed at 50 frames/s. Calibration was established from movement of the catheter tip positioned in the ventricle when the table was displaced by 8 cm. Extrasystoles and postextrasystoles were not studied. Multiple views of the coronary arteries and vein grafts, if present, were then obtained by Judkins's technique.

ANALYSIS OF ANGIOGRAMS

Cavity outlines were manually digitised frame by frame over each beat studied⁷ with a fixed external reference point. The timing of aortic valve opening and closure was established by direct inspection, and that of mitral valve opening was taken as occurring on the cine frame which first demonstrated unopacified blood within the left ventricular cavity at the onset of diastole. Ejection was defined as the time between aortic opening and closure, and isovolumic relaxation as the interval between aortic closure and mitral opening. Cavity volume on each frame was derived by the area-length method⁸ and plotted as a continuous curve, along with its first derivative with respect to time, to give peak rates of ejection and filling. The ejection fraction was calculated as stroke volume divided by end diastolic volume. End diastolic and end systolic volumes, ejection fraction, and peak ejection and filling rates of initial and final ventriculograms were compared in each patient. Two observers (KL and DG) digitised a total of 124 beats, and mean values from at least two beats were used for each determination.

Regional wall movement was demonstrated throughout the cardiac cycle by construction of isometric and contour displays.⁷ The method depends on constructing 40 plots of wall motion against time

from 40 points equally spaced around the cavity outline, starting from the junction of the mitral valve with the aortic root. Segments 1-15 represent the mitral valve and inferior wall, segments 15-25 the apical region, and segments 25-40 the free wall. The initial and final ventriculograms in each patient were compared with respect to the following features.

Hypokinesis was deemed to be present when the overall amplitude of inward motion between the start of the beat and mitral valve opening was less than the lower 95% confidence limits for the region in question determined from a series of ventriculograms in 20 patients without demonstrable cardiac disease. Wall motion during ejection was considered in the same way. If the overall amplitude of motion was ≤ 2 mm in either direction, the segment was considered to show *akinesis*. *Dyskinesis* was taken to be outward movement of more than 2 mm that occurred throughout ejection and lasted for at least 100 ms.

Abnormalities of isovolumic contraction—Two types were recognised: outward motion of ≥ 2 mm starting before aortic valve opening and persisting for no more than 60 ms into ejection, and early inward motion of ≥ 3 mm before aortic valve opening.⁹

Abnormalities of isovolumic relaxation—Again, these were of two types: abnormal inward motion of ≥ 2 mm,⁷ and outward motion of ≥ 7 mm. The latter abnormality was confined to segments 25-40 on the free wall.

The extent of each abnormality was determined from the number of segments for which values lay outside the 95% confidence limits of normal.

Assessment of change in regional motion

In order to describe any change in local wall motion patients were divided into three groups according to the findings at the initial angiogram: (a) those in whom the region of ventricle supplied by the thrombosed artery showed hypokinesis, akinesis, or dyskinesis only, a pattern of motion referred to as simple hypokinesis; (b) those in whom the affected region showed overall hypokinesis or dyskinesis, but in addition, there was abnormal inward wall motion during isovolumic relaxation; and (c) those in whom the affected region showed normal overall amplitude of motion, but in whom there was abnormal inward motion during isovolumic relaxation.

In each of these groups, regional wall motion was assessed in terms of amplitude and in terms of the four disturbances affecting the isovolumic periods. Based on previous studies of the reproducibility of the method of angiographic analysis,¹⁰ changes in regional amplitude of motion were regarded as significant when their extent around the cavity outline between the two angiograms differed by more

than four segments (that is by more than 10%), and when values moved from outside to inside normal 95% limits or vice versa, the former being considered an improvement and the latter a deterioration. Changes in wall motion during the two isovolumic periods were more complex to assess, since such asynchrony was regarded as being intermediate between normality and complete disappearance of function.³ Its loss might thus be a sign of either recovery or infarction. In order to resolve this difficulty, changes in the timing of wall motion were considered in conjunction with those of amplitude at the time of the second study. Only if amplitude was normal when asynchrony had resolved, was the change regarded as an improvement. Loss of asynchrony in the setting of persistent hypokinesis or akinesis was taken to represent part of the natural history of unmodified myocardial infarction.

ANALYSIS OF CORONARY ARTERIOGRAMS

Coronary arteriograms obtained during the first study before thrombolysis was performed were examined to determine which vessels were obstructed by thrombus and whether the other two main arteries were diseased. Collateral vessels were sought, and, when present, opacification of the occluded vessel itself was distinguished from that of its branches only. Arteriograms from the second study were examined to determine the state of the vessel in which flow was initially re-established and the presence, approximate severity of any underlying fixed stenosis, and, when present, a vein graft were noted. The state of the other vessels was also reassessed. In view of variability in the subjective analysis of coronary arteriograms,¹¹ stenoses were recorded as being mild or severe, with no attempt to quantify them in terms of percentage narrowing of the lumen. From this information, the affected artery was categorised as: (a) reoccluded or unchanged; (b) patent, but with a severe proximal stenosis, or (c) normal, with either a mild proximal stenosis or a functioning vein graft. Serum creatine concentration was measured⁶ and peak values were noted.

STATISTICAL METHODS

A paired Student's *t* test was used to compare differences between means. Differences between groups in the frequency of a single abnormality were examined by Fisher's exact probability test.

Results

CORONARY ARTERIOGRAPHY

In 19 out of the 23 cases flow was re-established in one of the three coronary arteries. In eight cases the right coronary artery was involved; three of these patients had important additional disease of one or more of the other two arteries. In four cases the circumflex artery was affected by thrombosis with other important disease in two cases, and in seven cases the anterior descending artery was thrombosed with additional disease in four. At the second study the thrombosed vessel remained patent in 16 cases, whereas in three (one right, one anterior descending, and one circumflex artery) it had occluded again. Collaterals were identified in seven cases; the distal segment of the occluded vessel was filled in five and branches only in two.

Examination of the arterial supply to the affected region at the second study showed that in six cases the situation was unchanged from that found on the first occasion, either because of unsuccessful thrombolysis or because of reocclusion (three cases each). In 11 cases there was an important proximal stenosis, and in six the arterial supply was uncompromised, either because there was a functioning vein graft (four cases) or because there was no important proximal stenosis (two cases).

OVERALL LEFT VENTRICULAR FUNCTION

The Table gives details of the results. There was no significant difference between the two studies for values of end diastolic or end systolic volume, ejection fraction, or peak ejection rate, although there was a consistent fall in peak filling rate by 160 ml/s ($p < 0.05$). Similar results were obtained when the

Table Overall left ventricular function before and after thrombolysis

	Normal	All patients		Improved flow		Flow unchanged	
		Before	After	Before	After	Before	After
End diastolic volume (ml)	150 (35)	180 (55)	170 (50)	170 (50)	160 (50)	200 (75)	190 (40)
End systolic volume (ml)	30 (15)	60 (35)	60 (40)	65 (35)	50 (80)	90 (70)	85 (50)
Ejection fraction (%)	65 (7)	62 (12)	66 (15)	62 (9)	69 (13)	57 (17)	58 (18)
Peak ejection rate (ml/s)	580 (210)	680 (200)	590 (240)	690 (190)	640 (230)	730 (270)	540 (250)
Peak filling rate (ml/s)	690 (260)	670 (220)	510 (200)*	660 (250)	540 (210)*	740 (220)	480 (160)

* $p < 0.05$ for change before and after thrombolysis.

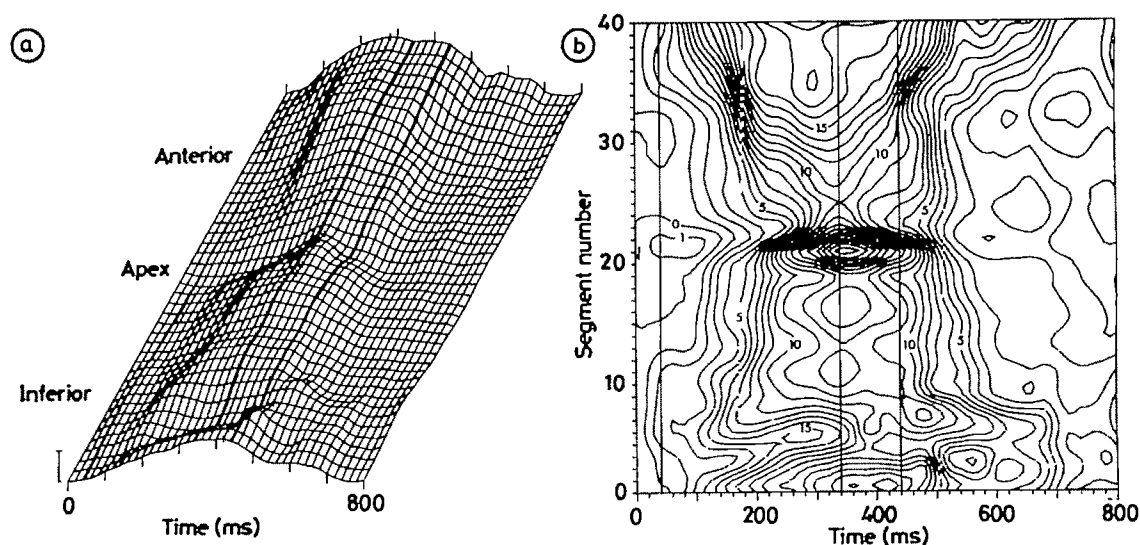


Fig. 1 Isometric (a) and contour (b) displays of regional left ventricular wall motion when left ventricular function is normal. Accentuated time markers (isochrones) represent aortic valve opening, aortic valve closure, and mitral valve opening. For description see text.

subgroup of patients in whom flow was re-established was considered separately, with the mean value of peak filling rate falling by 120 ml/s ($p < 0.05$). Patients with values outside the normal 95% confidence limit of normal at the first study were also considered separately. End diastolic volume was significantly increased in seven patients. It fell in six and was unchanged in one, the mean change being $-50(30)$ ml ($p < 0.05$). End systolic volume was increased in eight patients, and fell by a mean of $25(32)$ ml ($p < 0.05$). There was no significant change in ejection fraction in the subgroup of patients in whom values were reduced at the first investigation, whereas the 95% confidence limits of peak ejection and filling rate were so wide that all values fell within the normal range at the first examination.

REGIONAL WALL MOVEMENT

Normal. Figure 1 gives examples of isometric and contour displays of the left ventriculogram of a normal subject. On the isometric display (Fig. 1a) the horizontal lines represent the 40 plots of wall motion against time, inward displacement being represented as a curve upwards. Their origin from around the cavity outline is shown on the left. The diagonal lines are isochrones, joining events occurring simultaneously on each plot, one for each cine frame. The accentuated isochrones correspond to aortic opening, aortic closure, and mitral opening. The contour display is derived from the same information. Each

contour represents 1 mm of inward or outward movement of the endocardium from its position in the end diastolic frame. The three vertical lines again correspond to aortic opening and closure and mitral opening. In the normal subject there is no appreciable wall motion before aortic opening. During ejection, there is synchronous inward motion, as shown by the contour lines being almost vertical except for a small region at the apex. On the free wall, outward motion starts before mitral opening, and precedes that at the apex or along the inferior wall. After mitral opening, outward motion is rapid and synchronous, as shown by closely spaced and vertical contours.

Simple hypokinesia. In six patients in whom thrombolysis was achieved, and in whom the artery remained patent, simple hypokinesia was demonstrated at the first study in the region supplied by the thrombosed artery (four anterior descending, one right, and one circumflex artery). It remained unchanged at the second study in all. Figure 2 shows isometric and contour plots from a patient with a region of simple hypokinesia on the inferior wall between segments 10 and 15. The amplitude of inward motion is reduced to 4 mm. Its onset is delayed, but there is no significant movement in either of the two isovolumic periods. Motion in the rest of the cavity outline is normal, both with respect to amplitude and timing. The pattern at the later study (Fig. 2) is virtually unchanged. A minor diminution in amplitude on the anterior wall was noted,

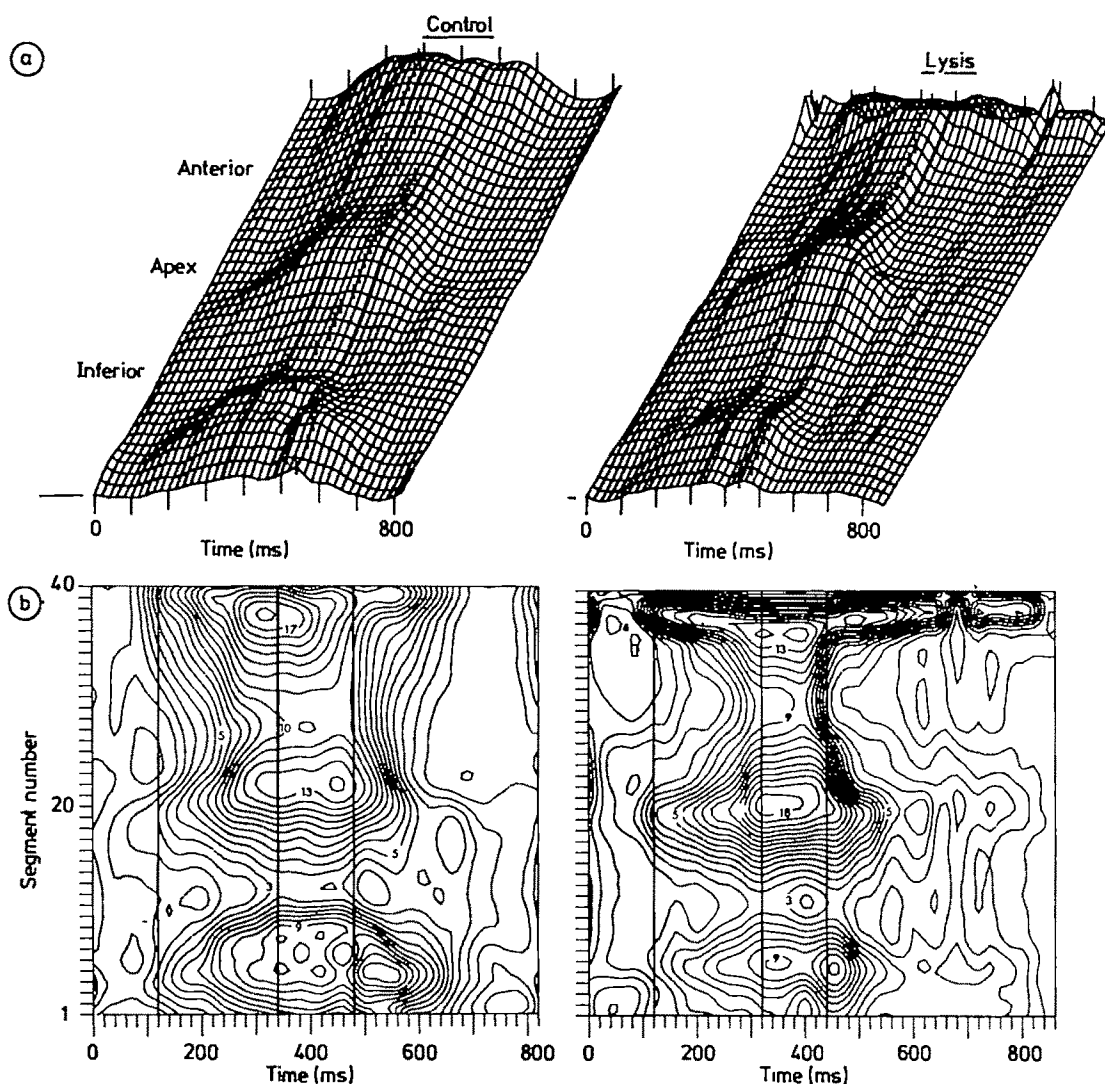


Fig. 2 Isometric and contour displays of left ventriculograms before (left hand isometric and contour displays) and after (right hand isometric and contour displays) thrombolysis from a patient with thrombosis of the circumflex coronary artery. There was a region of simple hypokinesis on the inferior wall which was unchanged at the second examination. For full discussion see text.

but this remained within normal 95% confidence intervals. Similar regions of simple hypokinesis were also unaltered in three cases in which the recanalised artery was occluded at the second study, and in two in whom thrombolysis had initially been unsuccessful. In one case in whom thrombolysis had been unsuccessful, but in whom a major stenosis of the anterior descending artery had been bypassed, the free wall (segments 20–30), which had been akinetic at the first study, returned to normal although

this was associated with the development of abnormal inward movement during isovolumic relaxation on the inferior wall (segments 8–20). Thus simple hypokinesis was present initially in 11 cases; it persisted unchanged in 10 despite successful thrombolysis in six, and was improved but did not return to normal in one with a vein graft.

Hypokinesis associated with delayed inward motion during isovolumic relaxation. This combination of abnormalities was present in six patients, three with

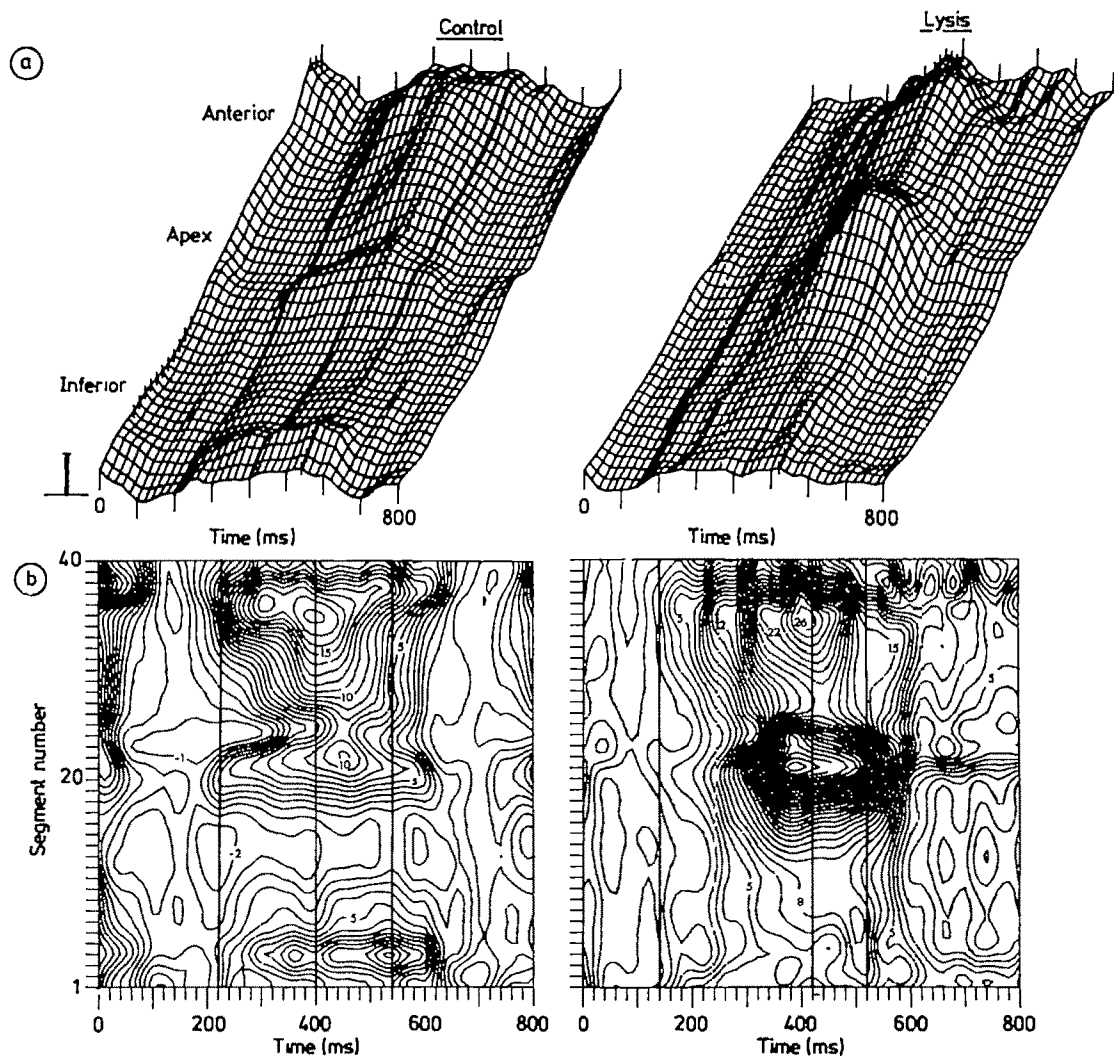


Fig. 3 Isometric and contour displays from a patient with thrombosis of the right coronary artery, in whom the control angiogram showed hypokinesis associated with delayed inward movement of the inferior wall. There was substantial improvement after thrombolysis. Layout as in Fig. 2. For full discussion see text.

disease of the right and three with disease of the anterior descending artery. Figure 3 shows results from a patient with right coronary artery thrombosis. In the first study (Fig. 3) there was a hypokinetic segment on the inferior wall, which showed a total inward motion of 4 mm, less than the normal lower 95% confidence interval, of which 2 mm occurs during isovolumic relaxation associated with a 10 mm early outward motion¹² along the free wall. During isovolumic contraction there is 2 mm abnormal outward movement along the inferior wall, associated with premature inward movement before aor-

tic valve opening on the free wall. At the second study (Fig. 3) the amplitude of movement in the inferior region had returned to normal. There was still some inward motion during isovolumic relaxation, but this was less extensive than in the earlier study and was almost completely confined to the region of the mitral valve. Wall movement during isovolumic contraction had become completely normal. There had thus been considerable improvement in regional wall motion in the inferior segment that was supplied by the affected coronary artery. In a second patient, who also had right coronary artery

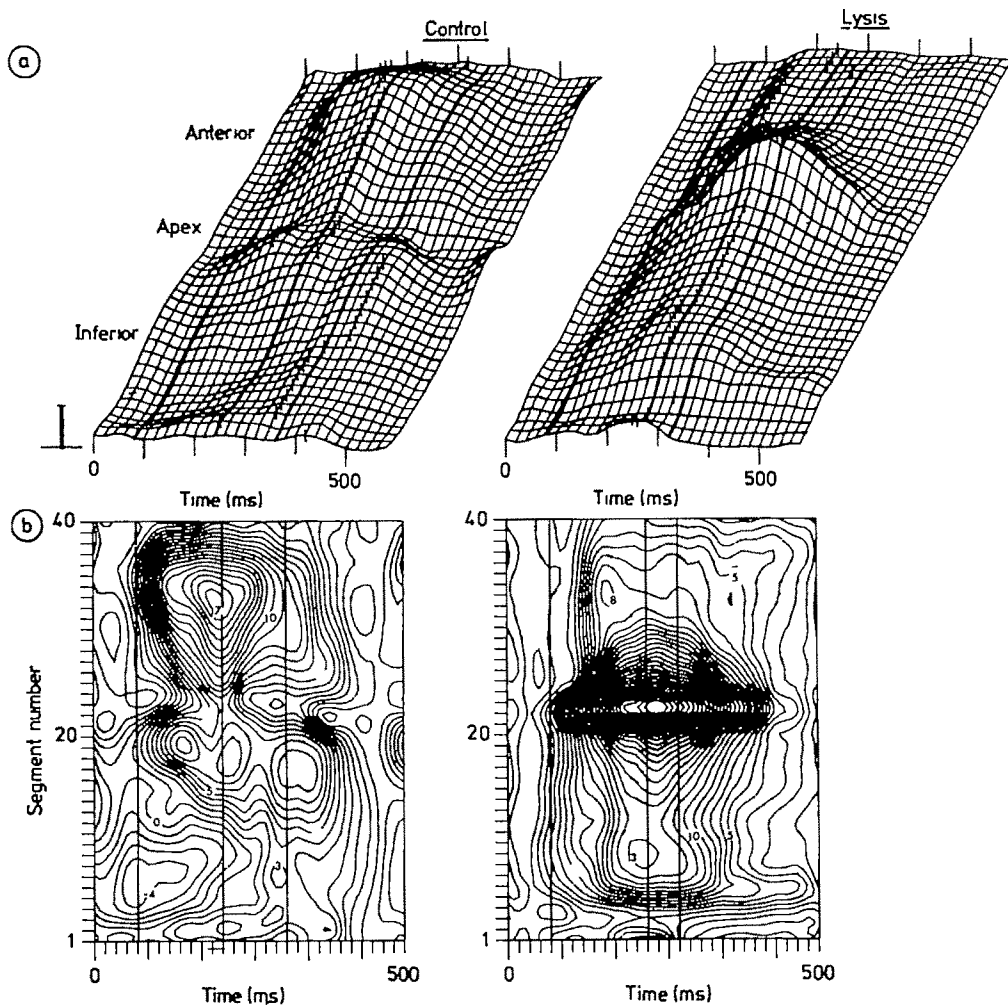


Fig. 4 Isometric and contour displays from a patient with circumflex coronary thrombosis showing delayed inward motion on the inferior wall and early outward motion on the free wall. Both these abnormalities have improved after thrombolysis. Layout as in Fig. 2 For full discussion see text.

disease, wall motion in the affected area returned completely to normal; the amplitude of motion had increased and the disturbance of wall motion during isovolumic relaxation was no longer apparent. One case, with anterior descending thrombosis, improved, with 3 mm of dyskinesia being replaced by 4 mm of inward motion. In three cases, the extent and distribution of the hypokinesia were unchanged, though inward movement during isovolumic relaxation was no longer apparent.

Inward motion during isovolumic relaxation with normal amplitude of wall motion. This pattern of wall motion was seen in eight patients, four with right, one with anterior descending, and three with

circumflex artery disease. In six the amplitude was normal over the whole segment, and in two over part of that showing asynchrony. Figure 4 shows the results from one of those with circumflex thrombosis. The earlier study (Fig. 4) demonstrated delayed inward motion in segments 5–12 along the inferior wall during isovolumic relaxation, though the total amplitude of inward movement was normal. At the same time, there was early outward movement along the free wall associated with hyperkinesis during systole. There was also early outward movement during isovolumic contraction in segments 4–9. Direct inspection of the two displays shows that movement of the inferior part of the ventricle over

segments 1–20 was delayed with respect to the free wall by approximately 150 ms throughout the whole cardiac cycle. After successful thrombolysis, the pattern of wall motion had become entirely normal in amplitude and timing. This response was seen in four further patients (two with thrombosis of the circumflex artery and two with thrombosis of the right coronary artery), but in the other three the abnormality of isovolumic relaxation persisted. Thus in 12 patients the affected area of myocardium showed delayed inward motion during isovolumic relaxation, with or without hypokinesis, which improved significantly in eight and reverted completely to normal in six. The effect of thrombolysis on segments with this pattern of motion thus differs significantly from that on segments showing simple hypokinesis ($p < 0.010$).

Additional abnormalities of wall motion amplitude.—Hyperkinesis was present in five patients at the time of the first study and dyskinesis in three (in two as an isolated abnormality and in one in association with abnormal inward motion during isovolumic relaxation). Neither abnormality was present in any patient at the time of the second study.

Additional abnormalities of wall motion during the two isovolumic periods.—Additional abnormalities of wall motion during the two isovolumic periods were also considered in association with the amplitude of wall motion in the region supplied by the affected coronary artery. Early outward wall motion during isovolumic relaxation reverted to normal in all of five patients who initially had thrombosis of the right or circumflex coronary artery; in four this was associated with a normal amplitude of wall motion in the inferior region and in one with akinesis. It appeared de novo in the second study in a patient in whom the affected vessel had become reoccluded and in whom akinesis persisted in the region supplied by the occluded vessel. In seven patients (four with thrombosis of the right coronary artery and three with thrombosis of the circumflex coronary artery) there was early outward motion along the inferior wall during isovolumic contraction. In five it disappeared as overall amplitude of motion in the affected region returned to normal. In two, in whom amplitude also remained unchanged, it did not. Early inward movement along the free wall during isovolumic contraction was seen only in those patients with simultaneous outward motion on the inferior wall. It returned to normal after thrombolysis in all but one case.

Relation of changes in wall motion to peripheral arterial supply.—In six patients the arterial supply to the affected region of ventricle was essentially unchanged at the second examination, either because of failure of thrombolysis or because of reocclusion.

In five of these patients, hypokinesis was present at the initial examination, with or without evidence of asynchrony, and this feature persisted, unchanged in distribution, at the second examination. In one case an isolated abnormality of isovolumic contraction returned to normal. Thus one out of six cases showed improvement. In 11 patients blood supply to the affected region was restored at the second examination but there was a major proximal stenosis. In four of these the amplitude of movement returned to normal, but in three asynchrony persisted (one in isovolumic contraction and two in isovolumic relaxation). In the remainder, hypokinesis persisted unchanged, with loss of asynchrony in two. In this group, therefore, appreciable improvement was seen in four, while seven remained unchanged. In five patients a normal or virtually normal arterial supply was restored. There was considerable improvement in wall motion in all. In two, hypokinesis associated with asynchrony became completely normal, in two isolated asynchrony became normal, and in one isolated hypokinesis was converted to normal amplitude but asynchrony developed. These differences in the incidence of improvement in relation to blood supply were statistically significant ($p < 0.007$). Changes in the pattern of wall motion were also related to the peak serum creatine kinase concentrations recorded during the acute illness. In the patients in whom there had been no change in wall motion at the second study, peak serum creatine kinase was 2010 (1450) U/l. This was significantly greater than in patients in whom improvement was seen (1290 (800) U/l ($p < 0.05$)) and in those in whom wall motion became normal (810 (510) U/l ($p < 0.01$)). No aspect of regional wall motion could be related to the presence or absence of collateral vessels at the first study or to the time after the onset of symptoms at which reperfusion was achieved.

Relation between wall motion and the first study and success of thrombolysis.—Thrombolysis was unsuccessful in seven patients either because flow was not re-established (four cases) or because the vessel had become reoccluded by the second study (three cases). In six of these cases, there was hypokinesis with no evidence of asynchrony. In the remaining cases in which thrombolysis was successful and the vessel remained patent at the second study,¹³ there was asynchrony during isovolumic contraction or relaxation in 11. This difference is significant ($p < 0.025$).

Discussion

The aim of thrombolysis is to re-establish flow to ischaemic regions of the ventricle and so to preserve myocardial function that would otherwise be lost. If

the procedure is to be of any clinical value it must improve left ventricular function. Such an improvement may be difficult to document because measurements before and after thrombolysis are made under widely different physiological conditions. Impending infarction is likely to be associated with increased autonomic activity resulting from various stimuli both cardiovascular and psychogenic. These affect cardiac output, heart rate, inotropic state, and peripheral impedance to which all commonly used measures of left ventricular function are sensitive. Differences in the pattern of left ventricular wall motion between the two studies must therefore be interpreted with caution, particularly when changes within the normal range occur.

The effect of thrombolysis on ejection fraction has been widely studied. The lack of change previously reported in the present group of patients⁴ was confirmed in later studies.¹⁴⁻¹⁶ Other responses of ejection fraction to thrombolysis have been described, including an increase conditional upon the presence of collateral vessels,^{13,17} or a consistent increase^{18,19} seen even when treatment is delayed by up to 18 hours after the onset of symptoms. One possible reason for ejection fraction failing to rise is that impaired function in one region of the ventricle is often accompanied by hyperkinesis elsewhere, which, in common with others,^{15,20} we found at the second study had regressed. Normal values in the acute phase and the frequent occurrence of spontaneous change²¹ were further reasons for ejection fraction being an insensitive index of the effects of thrombolysis. Other measures of overall left ventricular function were no more helpful. End diastolic and end systolic volumes were usually within the normal range, although they did tend to return towards normal if they were initially increased. Peak ejection rate was unchanged between the two studies, while the peak filling rate tended to fall, whether or not patency was achieved or maintained. We conclude that ejection fraction and other measures of overall left ventricular function are of only limited value for following the effects of thrombolysis.

Striking changes in regional wall motion occurred after thrombolysis; these depended on the pattern present at the initial study. After thrombolysis segments showing asynchrony were more likely to return to normal motion than those showing simple hypokinesis. Even within the group of patients with asynchrony, improvement was more likely if overall amplitude was initially normal rather than reduced. These differences in the incidence of improvement suggest a hierarchy of levels of impairment of ventricular function that are reflected in wall movement. It appears that ischaemic injury first shows itself as asynchrony rather than any change in amplitude.

Overall amplitude drops only when the injury is more severe, although even at this stage asynchrony may persist as evidence of residual contractile activity, showing itself most characteristically as inward movement during isovolumic relaxation. Segments showing simple hypokinesis, akinesis, or even dyskinesis if the free wall of the ventricle is affected, have suffered a degree of injury from which they are unlikely to recover even if the circulation is restored. Analysis of regional movement, therefore, can indicate segments which have undergone a comparable degree of injury, and the factors affecting the extent of recovery can be identified. Of these the most important seemed to be the extent to which flow to the affected region had been re-established, since wall motion was much more likely to return to normal when the arterial supply was uncompromised. We did not find the same absolute dependence of improvement on vein grafting reported by Sheehan *et al*,²² though the general principle of ensuring an adequate blood supply to affected areas was confirmed. A second factor was the peak level of serum creatine kinase activity, but there was no relation between the frequency recovery and the time from onset of symptoms to re-establishment of flow. Somewhat unexpectedly the presence of simple hypokinesis at the initial study proved to be a predictor of whether thrombolysis would be successful. This finding suggests that when myocardial function is irreversibly damaged, the integrity of the microcirculation itself is lost, so that even when the thrombus is lysed peripheral runoff is usually inadequate to maintain patency. Such a relation between initial wall motion and subsequent outcome of thrombolysis would invalidate the use of patients in whom lysis was not achieved as controls for assessment of the effects of the procedure on the left ventricular function in those in whom it was successful. Finally, these conclusions are not comparable with those based on the two frame method of analysis of regional wall motion. In this technique single frames corresponding to end systole and end diastole are identified so that regions showing asynchrony would be classified as either normal or hypokinetic depending on the frame chosen as "end systolic."²³ Similarly, regions showing asynchrony with reduced overall amplitude would not be distinguished from those showing simple hypokinesis by this method. Our results are thus not comparable with those in which wall motion is analysed in terms of regional ejection fraction,⁴ hemichord shortening,^{14,24,25} or the "center line" technique,²⁰ all of which are based on observations of only two frames. Rather, our results indicate the potential advantages of distinguishing abnormalities of amplitude from those of timing, which can only be achieved by considering

al. the frames in the cardiac cycle.

The present study was an exploratory one. It was retrospective and contained no control group to allow for the effect of spontaneous recanalisation or changes in ventricular function occurring between the two studies. It does not therefore confirm or refute the therapeutic effectiveness of thrombolysis. It does, however, suggest that a more elaborate analysis of regional wall motion than is usually undertaken may be helpful in such cases, in which a major objective is to detect and salvage compromised myocardium. If asynchrony is the hallmark of such areas, ability to locate it and to follow its progress might have practical consequences in determining therapeutic strategy in individual patients. It might be possible on the basis of the pattern of regional wall motion to exclude cases in whom success was unlikely, to identify those in whom myocardium was potentially salvagable even more than six hours after the onset of symptoms, or to follow the effects of less elaborate procedures such as intravenous thrombolysis. This information is potentially available non-invasively by digital subtraction or radionuclide angiography, and to a more limited extent by cross sectional echocardiography. Such imaging methods in combination with automatic boundary recognition and image analysis might provide a means by which these aims could be advanced.

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Exercise digital subtraction ventriculography for the detection of ischaemic wall motion abnormalities in patients without myocardial infarction

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SUMMARY Digital subtraction angiography permits high resolution imaging of the left ventricle after an intravenous injection of contrast medium. The capacity of digital subtraction angiography to detect ischaemic wall motion abnormalities was tested in 150 consecutive patients without myocardial infarction who were referred for coronary angiography. Digital ventriculograms were considered to be abnormal if there was a severe wall motion abnormality at rest or if segmental wall motion deteriorated after exercise. The global ventricular response to exercise was considered to be abnormal if the ventricular ejection fraction computed by the Dodge area length formula was $<50\%$ at rest or failed to increase after exercise. Seventy eight (52%) of these subjects had stenosis of $>50\%$ of at least one major coronary artery. In 36 (24%) more than one major coronary vessel was affected. Sensitivities for the detection of stenoses $>50\%$ coronary obstruction were 82% and 69% for an abnormal segmental wall motion response and an abnormal ejection fraction response respectively. The specificity of these test responses was 76% and 68% respectively. No complications resulted from the digital ventriculographic studies.

It is concluded that safe adequate digital ventricular imaging at rest and after exercise is possible and that an abnormal wall motion response is a sensitive indicator of important coronary obstructive disease.

Radionuclide ventriculography may be used to detect the exercise induced changes in left ventricular wall motion that indicate myocardial ischaemia. Early studies reported that it had a high sensitivity and specificity for the prediction of severe coronary obstructions.¹⁻³ Cross sectional echocardiography⁴⁻⁶ has shown promise as a technique for the study of left ventricular function after exercise, but it has low spatial resolution and it can be difficult to obtain adequate images in some patients. Digital subtraction ventriculography gives high resolution images of the left ventricle after intravenous injection of contrast. It may be able to detect exercise induced wall motion abnormalities caused by myo-

cardial ischaemia after exercise.⁷ We have tested this hypothesis.

Patients and methods

STUDY GROUP

Between November 1982 and April 1984 all consecutive patients referred to a group of participating cardiologists were screened for this investigation. Patients were excluded if they had a history of a myocardial infarction or diagnostic Q waves on their electrocardiogram. Diabetics on insulin (18) and those with evidence of valvar disease or cardiomyopathy (5) were also excluded as well as those with unstable angina (15) and those who refused to participate (16). In 157 patients resting and exercise digital subtraction ventriculography was successfully completed. In six patients the test was not completed—in three because we could not locate an adequate peripheral vein for catheter insertion and

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because diagnostic studies after exercise were inadequate in three. Seven subjects did not undergo coronary angiography (five with low probability of disease and two who refused). One hundred and two of the remaining 150 subjects were men and 48 were women (mean age 54 years). All of these subjects underwent selective coronary angiography within three days of their exercise ventriculograms. Seventy eight (52%) subjects were referred for coronary angiography because of chest pain that was typical of angina pectoris (pain in the upper part of the body precipitated by exertion and relieved within 20 minutes by rest). Sixty two (41%) subjects had atypical chest pain and ten subjects (7%) were symptom free. These latter subjects had been referred for angiography because of abnormal stress tests.

RESTING AND EXERCISE VENTRICULOGrams

The examinations were performed with a Philips Optimus M200 generator (continuous mode), a Philips 35/150 x ray tube, a caesium iodide image intensifier, a 525 line interlaced television camera, and a Philips DVI 1 videoprocessor. This system incorporates a dual-selectable aperture for the television camera that allows the operator to compensate manually for and reduce exposure to very large patients. Brass plate boluses placed over the x ray tube further reduce patient radiation dose, which is between 2000 and 4000 mR for an average study.

A 320 ms average mask was used for both resting and exercise studies. Mask acquisition was followed immediately by the injection of 40 ml of Renografin-76 through a 24 inch 16 gauge end hole catheter into the superior vena cava at a flow rate of 10–15 ml/s. X ray exposure settings were the same for the resting and exercise studies in each patient. A nine inch image intensifier was used for all but five studies in which a six inch camera was used because of small cardiac size. The x ray voltage was kept between 70 and 95 kV, and current between 50 and 100 mA. Continuous image acquisition at 30 frames/s ran for 15–25 s for resting studies and 10–16 s for exercise studies. A 512 × 512 pixel matrix was used. For both rest and exercise studies, image acquisition continued for a few seconds after the clearance of contrast from the left ventricle. These post-contrast frames were used for second order resubtraction. Three quarter inch videotape was used as the intermediate medium.

Resting studies were performed with the patient in the supine position and the right anterior oblique projection at held inspiration. The exercise bicycle was then moved into place and the patient's feet raised into the stirrups. The patient was then carefully instructed on the breath holding exercises that were needed for adequate images to be obtained

after bicycling had stopped. Exercise started at 25 W and was increased by 25 W every 2 min. The electrocardiogram was monitored on leads II, aVF, and V5 throughout exercise. Pulse and blood pressure were monitored every 2 min. Exercise was stopped because of exhaustion, dyspnoea, progressive angina, or leg pain and fatigue.

Immediately after the end of exercise the subject was asked to hold his breath at deep inspiration (2–4 s). Under fluoroscopic guidance the x ray image intensifier was repositioned. The subject was then allowed to exhale and again inhale deeply and hold his breath. A mask image was then taken, the subject was told to breathe normally, and contrast was injected. Subtracted image acquisition and fluoroscopy began immediately before the contrast injection so that the progress of the contrast bolus and the movements of the diaphragm could be monitored. As soon as the bolus had cleared the right ventricle, the subject was instructed to inspire deeply and hold his breath a third time. A few seconds after the contrast had cleared from the left ventricle, image acquisition was stopped and the patient was able to breathe normally.

The resting and exercise ventriculograms were immediately reviewed to determine their diagnostic adequacy. Electronic contrast enhancement and mask resubtraction were applied to enhance the visualisation of the endocardial edges. This remasking used mask images that followed the clearance of iodinated contrast from the left ventricle. All resting studies were considered to be adequate after a single contrast injection. In six cases exercise studies had to be repeated to obtain adequate images.

CORONARY ANGIOGRAPHY

Between one and three days after the exercise digital subtraction ventriculographic study, selective coronary angiography was performed by the Sones's or Judkins's techniques.

TEST ANALYSES

Rest and exercise digital subtraction ventriculograms were interpreted by the consensus of two observers who were unaware of the clinical and angiographic data. The videotaped runs of ventriculographic images were post-processed as described above and analysed for the presence and severity of segmental wall motion abnormalities. Though misregistration artefacts are more common after exercise than during resting studies, the non-shifted mask resubtractions improve image quality sufficiently to allow diagnostic interpretation in 90% of cases. The left ventricle was divided according to the American Heart Association Qualitative Report-

ing System into five segments: anterobasal, anterolateral, apical, diaphragmatic, and inferobasal.⁸ Each segment was given a grade from 1 to 6 as follows: 1 normal contractility, 2 mild hypokinesis, 3 moderate hypokinesis, 4 severe hypokinesis, 5 akinesis, 6 dyskinesis. Resting and exercise digital subtraction ventriculograms were considered to be abnormal if any of the five segments were grade 4 or higher at rest or if the grade of any segment was higher at exercise than rest. To estimate inter-observer agreement, these visual assessments were repeated blindly by a third observer who was an experienced cardiac angiographer without extensive experience of interpreting digital angiographic studies.

The resting and exercise ventriculographic studies were transferred from videotape to an analytical image processor (Data General Nova/4) in 128 × 128 pixel format and global ejection fraction was calculated by means of MDS A2 software. The investigator who calculated the ejection fraction was also blinded to the clinical, angiographic, and wall motion results. End diastolic and end systolic image frames were taken to be those with the largest and smallest endocardial contours. The observer used a light pen to draw the endocardial perimeters. The computer then calculated the ejection fraction by means of the Dodge area length formula. Ejection fractions which were <50% at rest or failed to increase with exercise were considered to represent abnormal responses.⁷

Selective coronary cineangiograms were interpreted by experienced angiographers not directly involved in the study protocol. These cardiologists were not told the results of the exercise studies although they were aware of the clinical data.

Results

ADEQUACY OF EXERCISE

The mean duration of supine bicycle exercise was 6.8 min (range 3.5 to 13.5). Forty eight (32%) subjects complained of exercise induced chest pain during the test. Seventy six (51%) subjects had exercise induced ST depression of >1 mm during the test. The mean heart rate achieved was 133 beats/min, the mean peak systolic blood pressure was 180 mm Hg, and the mean rate pressure product at peak exercise was 23 884 beats × mm Hg per minute.

ANGIOGRAPHIC RESULTS (DISEASE SEVERITY)

Seventy eight (52%) patients had important coronary disease defined as at least one stenosis producing >50% obstruction of a major coronary vessel. Thirty six subjects (24%) had a >50% obstruction of more than one vessel (multivessel disease). Twenty two had double vessel and 12 had triple vessel disease. Two subjects had a stenosis of ≥50% in the left main coronary artery.

OBSERVER AGREEMENT

In 80% (120/150) of cases the third independent observer agreed with the consensus assessments of the first two observers on the presence or absence of a resting or exercise wall motion abnormality. Agreement was slightly higher (81%) in studies of subjects without coronary artery disease than it was in those with coronary artery disease (78%).

SENSITIVITY AND SPECIFICITY OF EXERCISE VENTRICULOGRAPHIC RESULTS

Tables 1 and 2 show the comparative sensitivities and specificities of the various exercise ventricu-

Table 1 Important disease: any obstruction >50%

	Electrocardiogram > 1 mm ST depression (%)	(A) Resting wall motion abnormality (%)	(B) Exercise induced worsening of wall motion (%)	A or B (%)	Rest ejection fraction < 50% or exercise ejection fraction ≤ rest ejection fraction (%)
Sensitivity	56 (44/78)	24 (19/78)	76 (59/78)	82 (64/78)	69 (54/78)
Specificity	56 (40/72)	96 (69/72)	79 (57/72)	76 (55/72)	68 (49/72)

Table 2 Multivessel disease: obstruction of >50% in more than 1 vessel

	Electrocardiogram > 1 mm ST depression (%)	(A) Resting wall motion abnormality (%)	(B) Exercise induced worsening of wall motion (%)	A or B (%)	Rest ejection fraction < 50% or exercise ejection fraction ≤ rest ejection fraction (%)
Sensitivity	64 (23/36)	39 (14/36)	81 (29/36)	89 (32/36)	75 (27/36)
Specificity	54 (61/114)	93 (106/114)	61 (69/114)	57 (65/114)	56 (64/114)

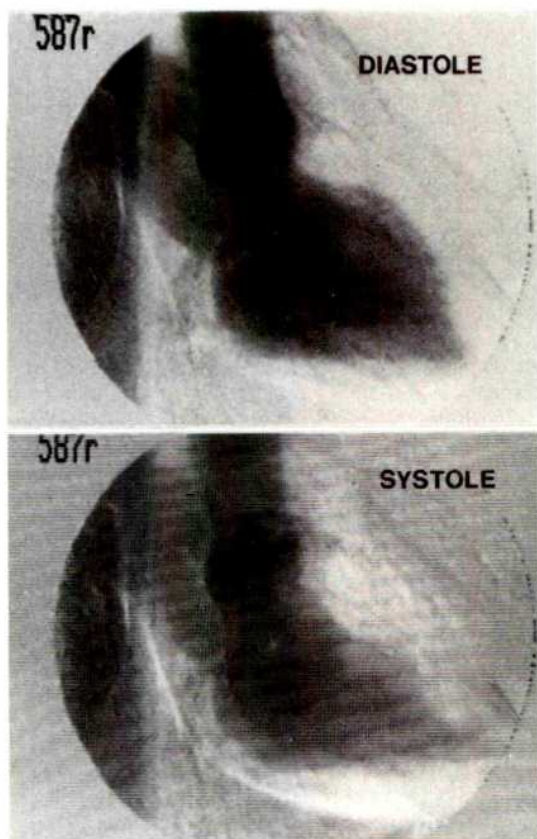


Fig. 1 Resting digital subtraction ventriculogram in a 60 year old man without a history or electrocardiographic evidence of myocardial infarction. Note akinesis of the inferior wall.

lographic and electrocardiographic variables used to detect important disease and multivessel disease respectively.

There were resting wall motion abnormalities (at least grade 4) (Fig. 1) in 24% of subjects with important disease and in 39% with multivessel disease. Such resting abnormalities occurred in only 4% of subjects without important coronary obstructions. Exercise induced a worsening of segmental wall motion (Fig. 2) in 76% of subjects with important disease and in 81% of subjects with multivessel disease. Either a severe resting wall motion abnormality (at least grade 4) or an exercise induced worsening of wall motion occurred in 82% of subjects with important disease and in 89% of subjects with multivessel disease. Neither resting nor exercise induced wall motion abnormalities (Fig. 3) were present in 76% of subjects without important coronary obstructions.

EJECTION FRACTION RESPONSE

The mean ejection fractions at rest and at peak exercise in patients with important coronary obstructions were 73.3 and 67.5 respectively ($p < 0.01$). For those subjects who did not have important coronary obstructions, the resting and exercise ejection fractions were 78.7 and 80.1 ($p = 0.14$). Sixty nine per cent of the subjects with important coronary obstructions had a resting ejection fraction $< 50\%$ or they failed to increase their ejection fraction with exercise, while 75% with multivessel disease had abnormal ejection fractions. Of those subjects without any important coronary obstructions, 68% had normal rest and exercise ejection fractions. Thus both the sensitivity and specificity of abnormal ejection fractions were less than the sensitivity and specificity of segmental wall motion abnormalities.

Because many cardiologists refer their patients with typical angina pectoris directly for cardiac catheterisation without preliminary testing, we divided our study group into subgroups with and without a history of typical angina pectoris. Of those with typical angina pectoris, 76% (59/78) had important coronary artery disease. Of those without angina only 26% (19/72) had important coronary obstructions. The sensitivity of exercise digital subtraction ventriculographic wall motion abnormalities for the detection of important coronary artery disease was 0.83 (49/59) for patients with angina and 0.79 (15/19) for those without angina. The respective specificities were 0.84 (16/19) and 0.74 (39/53).

LOCALISING CORONARY ARTERY OBSTRUCTIONS

In order to determine whether obstructions of the left anterior descending coronary artery caused anterior segmental wall motion abnormalities and obstructions of the right coronary artery caused inferior abnormalities, we calculated the sensitivities and specificities of anterior and inferior segmental abnormalities for the prediction of significant coronary obstructions in the respective coronary arteries. Of 53 subjects with important disease in the left anterior descending coronary artery, 39 (74%) had an anterior wall motion abnormality. Of 97 subjects without disease in the anterior descending, 67 (69%) did not have an anterior abnormality. Of 37 subjects with important obstructions in the right coronary artery, 26 (70%) had a motion abnormality in one of the inferior segments. Of 114 subjects without right coronary artery disease, 106 (93%) did not have an inferior abnormality. Obstructions of the circumflex coronary artery might be expected to cause wall motion abnormalities not visible in the right anterior oblique projection. For this reason, we calculated the sensitivity of segmental wall motion abnormal-

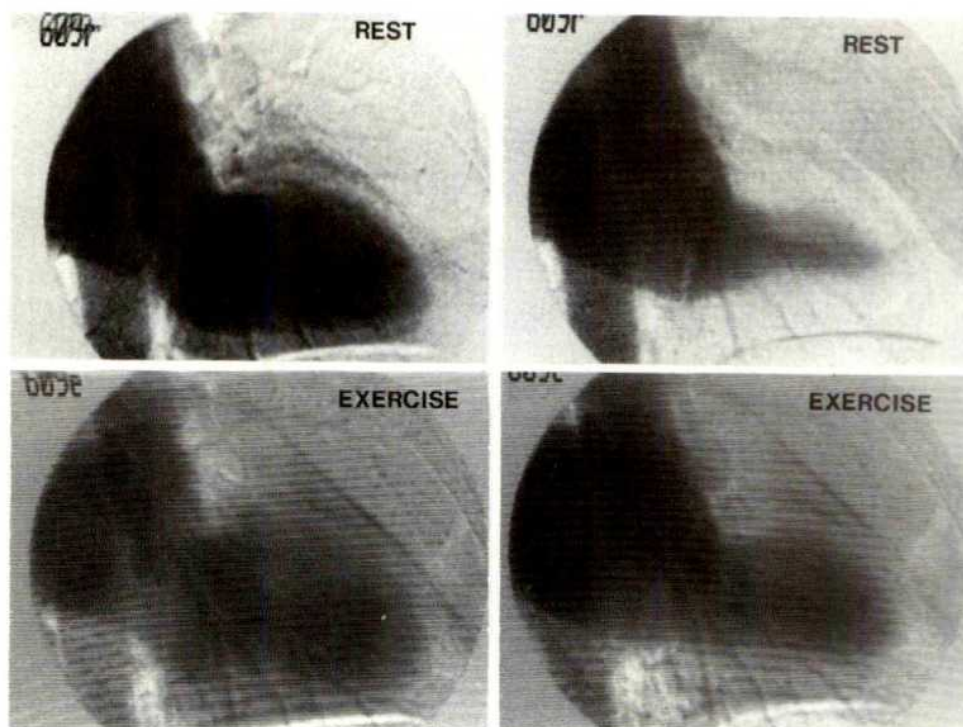


Fig. 2 Resting and exercise digital subtraction ventriculograms of a 48 year old man with disease in the anterior descending and circumflex coronary artery. Note normal end diastolic (left) and end systolic (right) outlines at rest. After exercise, systolic outline shows hypokinesis of the anterior wall and apex.

ities for the prediction of important disease in the circumflex artery. Thirty six subjects had important obstruction of the circumflex coronary artery. Thirty two (89%) had segmental wall motion abnormalities in the right anterior oblique projection.

Discussion

The results of this investigation suggest that exercise digital subtraction ventriculography is a sensitive method for detecting ischaemic wall motion abnormalities produced by coronary obstructions in patients without previous myocardial infarction. Its specificity and its accuracy in localising coronary obstructions are not as impressive as its high sensitivity.

In this investigation subjective analysis of wall motion at rest and after exhausting exercise was more accurate in predicting important coronary obstruction than was an abnormal resting ejection fraction or an exercise induced change in ejection fraction. This result is contrary to that of other

investigators who used resting and exercise radionuclide ventriculography to predict important coronary artery disease.⁹ Though one explanation of this discrepancy may derive from the choice of patients without infarction, we can suggest three possible explanations. First, the high spatial resolution of radiographic images compared with the relatively low resolution of radionuclide images might explain the high sensitivity of digital ventriculography in the detection of segmental wall motion abnormalities. A possible explanation for the relatively poor performance of the ejection fraction response to exercise might be the use of the Dodge single plane area length formula. This method of determining ejection fraction was standardised on resting ventriculograms in subjects with relatively normal hearts.¹⁰⁻¹² Segmental wall motion abnormalities caused by coronary artery disease reduce the accuracy of the Dodge method.

Gibbons *et al* have reported a high false positive rate of the ejection fraction response in patients with normal coronary arteries, especially in women and in

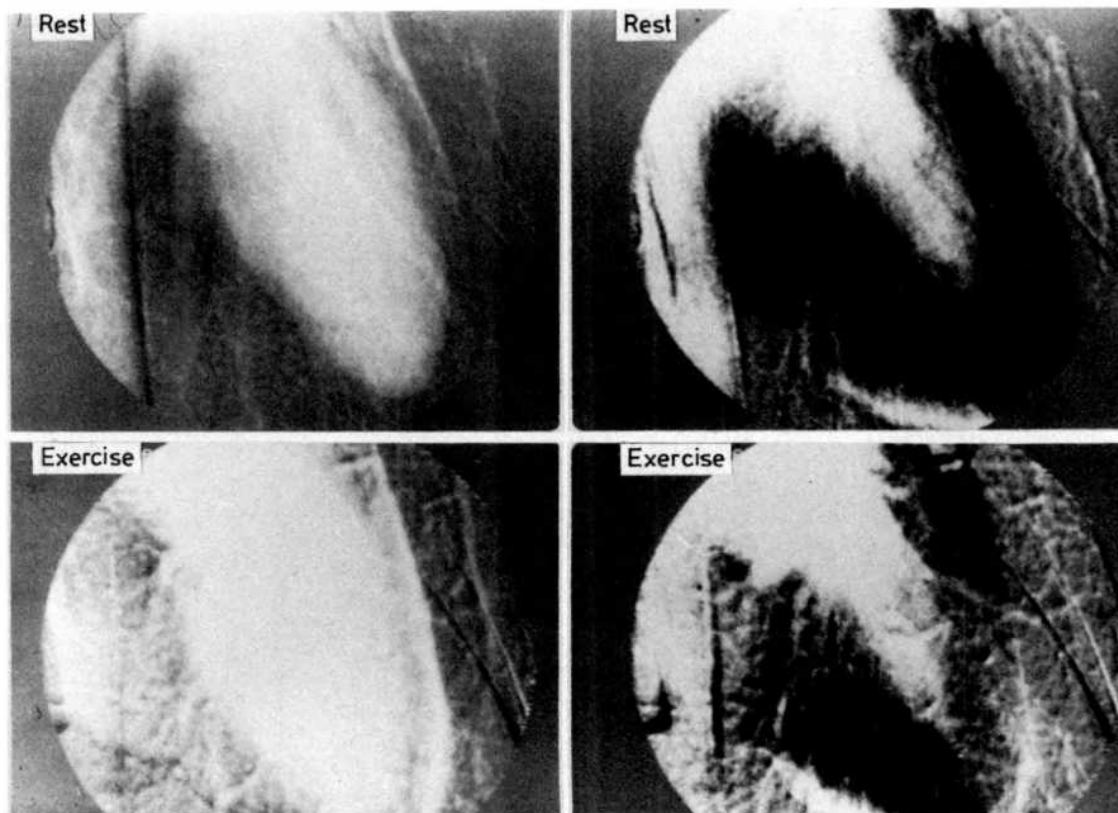


Fig. 3 Normal resting and exercise ventriculograms in a 43 year old woman with atypical chest pain and normal coronary arteries.

subjects with low resting ejection fractions.¹³ Inclusion of these patients might account for the low specificity of the ejection fraction in our investigation.

The low sensitivity of the ejection fraction response may also find an explanation in the delay between the completion of exercise and left ventricular imaging. This did not exceed 30 s in any case and was usually <15 s. Dymond *et al*, however, have reported that the sensitivity of the ejection fraction response is reduced when radionuclide ventriculography follows the completion of exercise by less than 15 s.¹⁴

Most of the patients studied were able to hold their breath long enough for adequate post-exercise studies to be performed. Post-exercise contrast injection was well tolerated and not often associated with complaints of flushing or nausea, as was the case with resting injections.

Despite the encouraging results of this investigation we do not believe that digital subtraction ventriculography should replace con-

ventional techniques of screening patients for coronary obstructions. Digital ventriculography has disadvantages that are not shared by other methods of exercise testing. Venous access was impossible in three subjects of this investigation. Three exercise studies could not be interpreted. The interobserver discordance was high (20%). Exercise digital subtraction ventriculography may be contraindicated in subjects with renal impairment and in those with severe cardiac failure. The radiation dose is considerably higher during digital subtraction ventriculography than during radionuclide examinations. High resolution continuous digital subtraction radiographic imaging is cumbersome and requires the use of an expensive angiographic laboratory. In the course of the present investigation no serious complications were encountered. There is, however, the possibility of serious angiographic contrast reaction. Further study and investigation are needed to determine the appropriate clinical and research applications of exercise digital subtraction ventriculography.

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Diagnosis of important fixed coronary stenosis in patients with variant angina by exercise tests after treatment with calcium antagonists

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SUMMARY A 12 lead electrocardiogram was recorded during treadmill exercise in 57 patients with variant angina in whom coronary angiography was performed. Thirty six patients performed exercise tests with and without calcium antagonists, and 21 performed them only with calcium antagonists. In 55 patients calcium antagonists had prevented spontaneous attacks of variant angina for more than two days before the test. The other two patients were given a single dose of diltiazem (90 mg) two hours before the test. Exercise testing without calcium antagonists induced ST segment elevation with chest pain in nine patients, ST segment depression in 10 (nine with chest pain), and no important shift of the ST segment in 17. Five patients had severe coronary stenosis ($\geq 75\%$) and all of them showed positive response. Thirty one patients had no important coronary stenosis and 14 of them showed positive response. The sensitivity of the exercise test in detecting a coronary stenosis $\geq 75\%$ was 100% without calcium antagonists but the specificity was low (55%). When the exercise test was done in patients taking calcium antagonists, only two (specificity 96%) of 48 patients without severe coronary stenosis showed positive response (elevation of ST segment in one and depression in another) whereas all nine patients with severe coronary stenosis had a positive response (depression of ST segment in six and elevation in three (sensitivity 100%).

It is concluded that exercise testing with calcium antagonists may be a useful method for detecting severe coronary stenosis in patients with variant angina.

Coronary lesions in patients with effort angina are reliably detected by exercise induced shifts in the ST segment.^{1,2} In variant angina, however, exercise causes coronary spasm in some patients and hence elevation or depression of the ST segment even in the absence of an important coronary lesion.³⁻⁹ For this reason exercise testing may not be helpful in the evaluation of coronary lesions in patients with variant angina. Reliable exercise testing depends on the complete prevention of coronary spasm during exer-

cise. Calcium antagonists prevent spontaneous and exercise induced coronary spasm.^{7,10} We have therefore evaluated the diagnostic value of exercise tests in variant angina in patients taking calcium antagonists and compared the result with that obtained when exercise testing was performed without calcium antagonists.

Patients and methods

PATIENT SELECTION

We studied patients with variant angina admitted to Kyushu University Hospital between 1976 and 1984. Variant angina was diagnosed when the patient showed transient ST segment elevation of ≥ 1 mm on a 12 lead electrocardiogram during chest pain at rest with no subsequent rise in serum enzyme

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concentrations. All 57 patients were assessed by both treadmill exercise test and coronary angiography. Thirty six patients underwent exercise tests with and without calcium antagonists and the remaining 21 only performed the test after taking calcium antagonists. Forty six were male and 11 were female (age range 31 to 70 years, mean (SD) 55 (9)). One patient had a history of previous myocardial infarction. All were in sinus rhythm and showed no arrhythmias before the exercise test.

All patients underwent coronary angiography by Judkins' or Sones' techniques. Multiple views of each vessel were filmed. When a lesion was noted, the vessel was filmed again in multiple views after administration of sublingual or intravenous glyceryl trinitrate. The coronary artery diameter was measured on the projected screen by means of slide calipers. Coronary stenosis was expressed as the reduction in diameter at the stenosis in relation to the mean diameter of two non-stenotic portions measured just proximal and distal to the stenosis. Patients were divided into three groups according to the degree of coronary stenosis. Group 1 (minimal) consisted of patients with normal coronary arteries or with stenosis of <50%. Group 2 (moderate) consisted of patients with coronary stenosis of 50%–74%, and group 3 (severe) had coronary stenosis $\geq 75\%$.

TREADMILL EXERCISE TEST

The treadmill exercise test was performed according to a Bruce or modified Bruce protocol. Exercise tests were performed between 7 am and 10 am. Medication with cardiovascular activity was withheld for at least two days before the test. An exercise test was performed one to three hours after oral administration of the calcium antagonist and no more than two weeks before coronary angiography; the interval between the two exercise tests ranged from two days to two weeks. Blood pressure and heart rate were measured every minute during exercise and the recovery period of 6–15 min. Three leads of a selected electrocardiogram were continuously monitored during exercise. A 12 lead electrocardiogram was recorded before the exercise and once a minute during the recovery period until the electrocardiogram reverted to normal, and also during chest pain. The end point of the exercise test was reached when (a) the submaximal heart rate (more than 85% of age matched maximal heart rate) was reached, (b) chest pain developed, (c) the ST segment changed by ≥ 2 mm, (d) exhaustion or leg fatigue developed, or (e) systolic blood pressure fell by ≥ 20 mm Hg. All patients reached the target heart rate or had chest pain during the exercise test.

ST segment changes were deemed to be positive

when horizontal or down sloping depression of ≥ 1 mm occurred or when ST segment elevation of ≥ 1 mm was seen. Informed consent was obtained from each patient before the exercise test and coronary angiography.

ADMINISTRATION OF CALCIUM ANTAGONISTS

Treadmill tests were performed 1–3 hours after oral administration of calcium antagonists—120 to 360 mg/day of diltiazem in 50 patients, 40 to 80 mg/day of nifedipine in two, 160 mg/day of nicardipine in two, and a combination of diltiazem 240 mg and nifedipine 40 mg/day as three or four divided doses in one patient. These doses abolished the rest angina as well as the painless ST segment elevation, which was confirmed by Holter electrocardiographic monitoring.¹¹ Calcium antagonists were given for ≥ 2 days before the exercise test. Ten of these patients were given 90 mg of diltiazem two hours before the test in order to achieve plasma concentrations in the therapeutic range.¹² Two patients had only one dose of diltiazem (90 mg) two hours before the treadmill test. Exercise tests were not performed for two hours after a meal. The 12 patients who were given an additional or single dose of 90 mg diltiazem were studied prospectively. The others were studied retrospectively.

STATISTICAL ANALYSIS

The diagnostic values of exercise tests with and without a calcium antagonist were compared by a χ^2 test with Yates's correction. The prevalence of positive response to exercise tests in the three groups of patients with different angiographic findings was analysed by the variance test for homogeneity of the binominal distribution.¹³ The pressure-rate product of exercise tests with and without calcium antagonist was compared by Student's *t* test for paired data. The pressure-rate products in the three groups with different angiographic findings were compared by analysis of variance. P values of <0.05 were considered to be statistically significant.

Results

Table 1 shows the clinical features of patients and their angiographic findings. Thirty six patients had normal coronary arteries or mild coronary stenosis (group 1) and 12 patients had moderate coronary stenosis (group 2). Nine had severe coronary stenosis (group 3); seven of them had single vessel disease and two had two vessel disease. Before admission 28 patients had only rest angina and 29 had both rest and effort angina. Most patients with severe coronary stenosis had both rest and effort angina. ST segment elevation that was typical of variant angina

Table 1 Patient profiles

	Coronary stenosis		
	Mild (<50%)	Moderate (50%-74%)	Severe ($\geq 75\%$)
Number of patients	36	12	9
Ages (mean (SD))	54 (10)	57 (5)	58 (7)
Sex (M/F)	27/9	10/2	9/0
Type of angina before admission:			
Rest angina	23	4	1
Rest and effort angina	13	8	8
Site of ST segment elevation during angina:			
Anterior leads	14	7	6
Inferior leads	19	5	3
Both	3	0	0
Previous myocardial infarction	0	0	1
Number of coronary arteries with $\geq 75\%$ stenosis:			
1 vessel	0	0	7
2 vessels	0	0	2
3 vessels	0	0	0

was seen in anterior leads in 27 patients, in inferior leads in 27, and in both in three.

Figures 1 and 2 show 12 lead electrocardiograms during treadmill exercise in a patient without and with calcium antagonists. Without calcium antagonists he complained of chest pain after 5 min of exercise on Bruce's protocol and transient ST segment elevation developed in leads II, III, and aVF (Fig. 1). A repeat exercise test also provoked chest pain with ST segment elevation. When an exercise test

was performed after he had taken a calcium antagonist, he could exercise for up to 9 min without chest pain or ST segment change (Fig. 2). Coronary angiography showed only a mild stenosis (25%) in the left anterior descending coronary artery.

Figures 3 and 4 show 12 lead electrocardiograms in another representative patient. During exercise

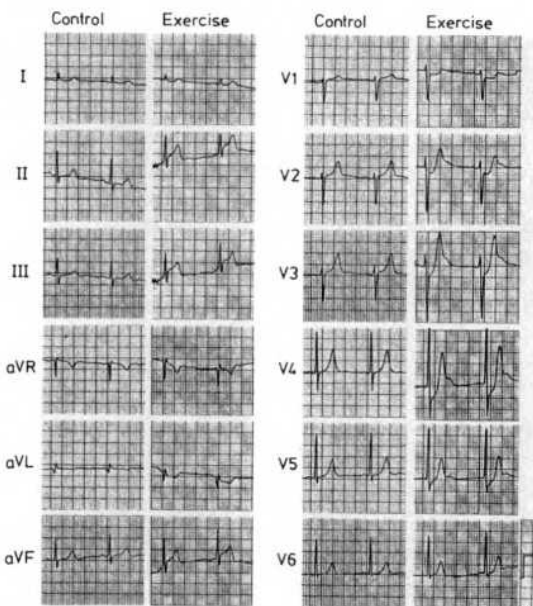


Fig. 1 Twelve lead electrocardiograms in a patient at rest and during chest pain after exercise. The exercise test was done without calcium antagonists. Chest pain was associated with the development of ST segment elevation in leads II, III, and aVF; and reciprocal ST segment depression in leads aVL and V1-V5.

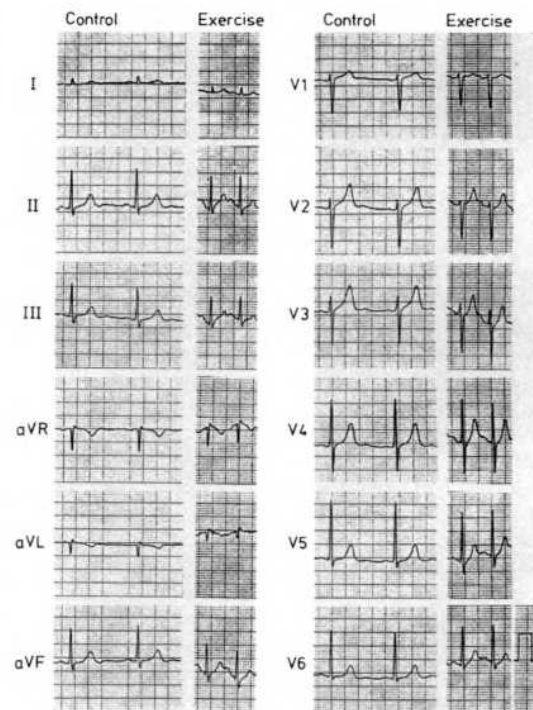


Fig. 2 Treadmill exercise test in the same patient as Fig. 1 while he was on a calcium antagonist. He attained age matched maximal heart rate without chest pain or ST segment shifts. Coronary angiography showed no important coronary stenosis in this patient.

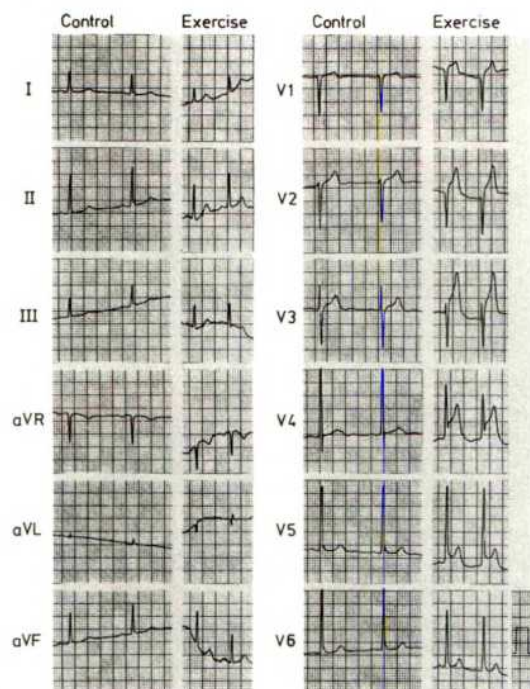


Fig. 3 Twelve lead electrocardiograms in a patient at rest and after exercise without calcium antagonists. An anginal attack developed with ST segment elevation in leads V1–V5.

tests performed without calcium antagonists he complained of chest pain after 3 min on the Bruce protocol and ST segment elevation developed in leads V1 to V5 (Fig. 3). Unlike the patient in Figs. 1 and 2 he had chest pain on exercise even after calcium antagonist had been given; ST segment depression developed in leads V4 to V6 (Fig. 4). Coronary angiography showed a 90% stenosis of the left anterior descending coronary artery.

EXERCISE TESTS WITH AND WITHOUT CALCIUM ANTAGONIST

Thirty six patients performed exercise tests without calcium antagonists; all of them had spontaneous attacks of angina that occurred a few times a month to several times a day. Nineteen of 36 patients responded positively to the exercise test. Nine of them had ST segment elevation and 10 had ST segment depression. Chest pain developed during 18 positive tests. Figure 5 shows the prevalence of positive response in the three groups of patients with different degrees of organic coronary stenosis. All five patients with severe coronary stenosis developed important ST segment shifts with chest pain and seven of the eight patients with moderate coronary

stenosis had a positive response. Seven (30%) of the 23 patients with normal coronary angiogram or mild coronary stenosis also showed a positive response, but this was significantly less common than the other two patient groups ($p < 0.025$).

Figure 6 shows the results of 57 exercise tests after calcium antagonists. All nine patients with severe coronary stenosis showed a positive response. But 11 of the 12 patients with moderate coronary stenosis did not develop significant shifts of ST segment or chest pain. Only one of the 36 patients with normal coronary angiogram or mild coronary stenosis responded positively. Positive responses were significantly more common in patients with severe coronary stenosis than in the other two patient groups ($p < 0.005$). Of the 11 patients with a positive response, four had ST segment elevation and seven had ST segment depression (Fig. 6). Nine patients had chest pain during the exercise test.

Figure 7 gives the sensitivity, specificity, and predictive value of the exercise test with and without calcium antagonists when it was used to diagnose severe coronary stenosis. The sensitivity of exercise tests without calcium antagonists was high (5/5,

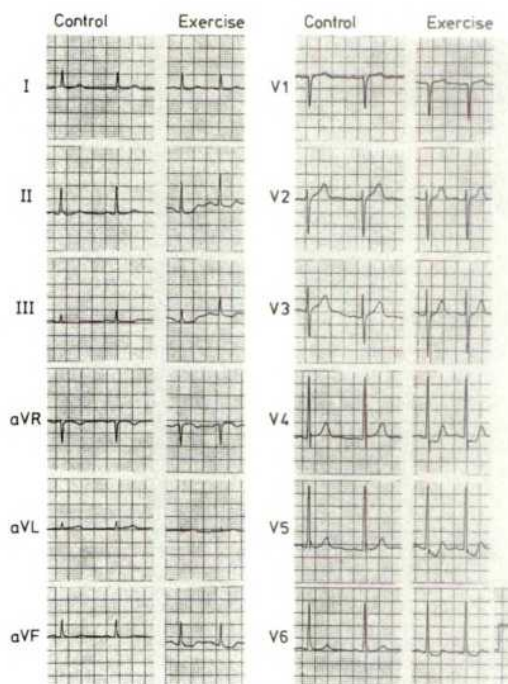


Fig. 4 Treadmill exercise test in the same patient as Fig. 3. Chest pain developed even with calcium antagonists, and ST segment depression was seen in leads V4–V6. He had severe coronary stenosis (90%) of the left anterior descending coronary artery.

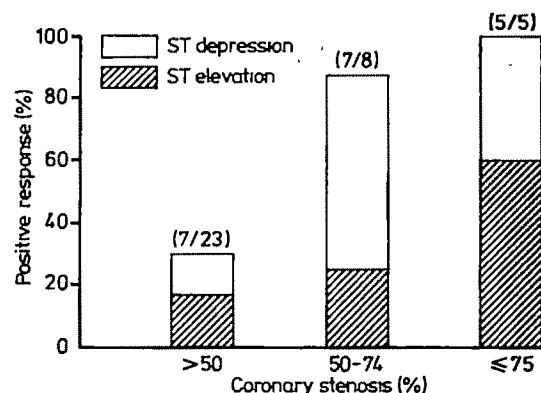


Fig. 5 Frequency of positive responses to treadmill tests in patients with variant angina. Treadmill tests were done without calcium antagonists. Patients were divided into three groups according to the degree of coronary stenosis. Numbers in parentheses are numbers of patients with a positive response as a fraction of those examined.

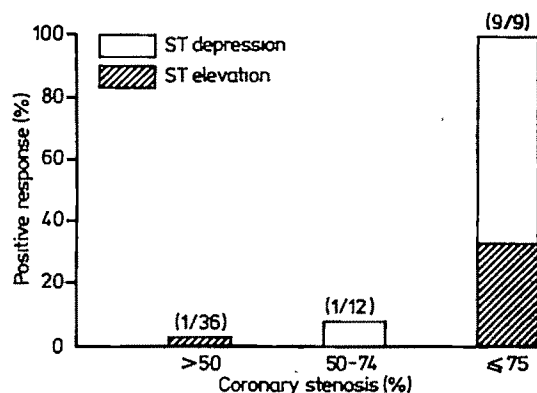


Fig. 6 Frequency of positive responses to treadmill tests in patients with variant angina. Treadmill tests were done with calcium antagonists. Patients were divided into three groups according to the degree of coronary stenosis. Numbers in parentheses are numbers of patients with a positive response as a fraction of those examined.

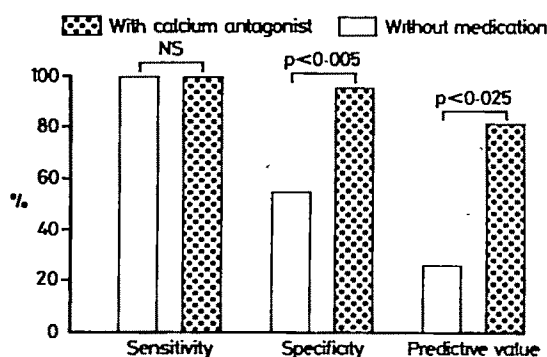


Fig. 7 Sensitivity, specificity, and predictive value of treadmill tests for the diagnosis of important coronary stenosis (75%). Treadmill tests with calcium antagonists showed significantly higher specificity and predictive value than did those without any medication.

100%). But false positive responses were common and the specificity and predictive value were low (17/31, 55%; and 5/19, 26% respectively). The false positive rate during exercise tests after calcium antagonists was low and the calculated specificity and predictive value were very high (46/48, 96%; 9/11, 82% respectively). The sensitivity was also high (9/9).

PRESSURE-RATE PRODUCT ATTAINED ON EXERCISE TESTING

Table 2 gives the pressure-rate product attained on treadmill tests in three different patient groups. The pressure-rate product was significantly lower in patients with a positive response than in those with a negative response. This was found in exercise tests both with and without calcium antagonists. In exercise testing without calcium antagonists patients with severe coronary stenosis tended to develop angina and/or ischaemic ST segment changes at a lower pressure-rate product (14700 (5000)); but this difference was not statistically significant. In patients with a negative exercise response the administration of calcium antagonist did not change the pressure-rate product.

Table 2 Pressure-rate product attained on exercise tests with and without calcium antagonists

	Coronary stenosis			Total
	Mild (<50%)	Moderate (50%-74%)	Severe (≥75%)	
Without calcium antagonist:				
Negative response	24800 (7090) (16)	33800 (1)	— (0)	25300 (7200) (17)
Positive response	19900 (5190) (7)	19500 (3450) (7)	14700 (5000) (5)	18400 (4870)* (19)
With calcium antagonist:				
Negative response	26000 (4950) (35)	25800 (2470) (11)	— (0)	26000 (4450) (46)
Positive response	16700 (1)	24800 (1)	17800 (3820) (9)	18400 (4040)* (11)

Values are mean (SD). Italic numbers in parentheses are number of patients.

*p < 0.01, compared with negative response group.

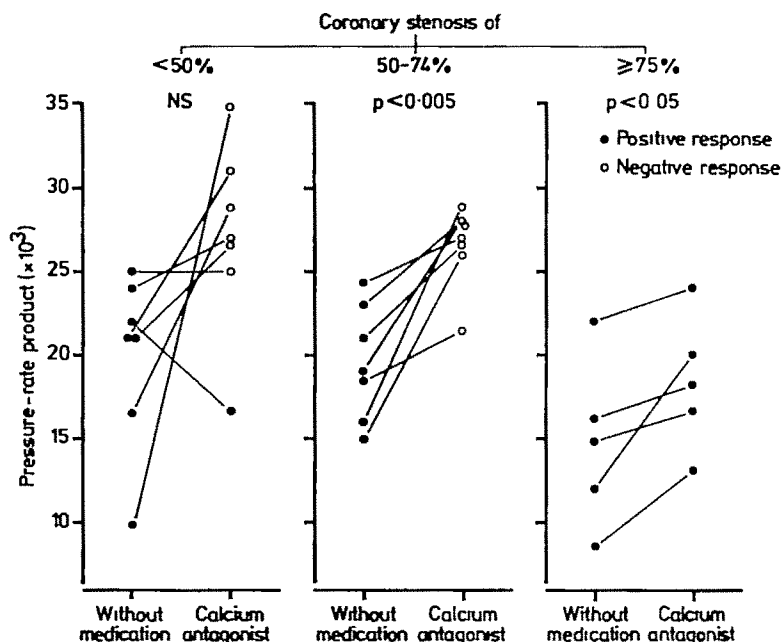


Fig. 8 Pressure-rate product in patients who responded positively to the exercise test without calcium antagonist and the change after calcium antagonists had been given. Closed circles indicate a positive response and open circles a negative response. In most patients without important coronary stenosis ($\geq 75\%$) the exercise response changed from positive to negative after calcium antagonist and a higher pressure-rate product was attained.

Nineteen patients showed a positive response to exercise testing without calcium antagonists. Figure 8 shows the pressure-rate product of each patient as well as changes in the product after calcium antagonists. With calcium antagonists the exercise tests resulted in a negative response in 13 patients and the pressure-rate product increased in 12 of these patients. One patient without severe coronary stenosis responded positively to the exercise test even with calcium antagonist and angina with ST segment elevation developed at an even lower pressure-rate product. The pressure-rate product in five patients with severe coronary stenosis increased slightly after calcium antagonists but remained low compared with that in other patients ($p < 0.05$ vs mild coronary stenosis, and $p < 0.01$ vs moderate coronary stenosis).

Discussion

Variant angina can be provoked by hyperventilation,¹⁴ alcohol,¹⁵⁻¹⁷ and intravenous administration of ergometrine¹⁸⁻²¹ or histamine.²² Several studies have also indicated that exercise can provoke

an anginal attack in some patients with variant angina.³⁻⁸ In other words some patients with variant angina develop chest pain with ischaemic ST segment shifts in the absence of severe coronary stenosis. For this reason the exercise test, which gives very useful information for the evaluation of coronary lesions in effort angina,^{1,2} seems to be of limited value in patients with variant angina. In the present study 14 of 31 patients without severe coronary stenosis developed angina or ST segment changes or both during treadmill exercise tests. This result is compatible with that reported by Waters *et al.* In their study important coronary stenosis was defined as narrowing of $\geq 70\%$ and 19 of 41 patients without coronary stenoses developed important ST segment shifts on exercise.⁷ Fukami *et al* reported a similar result.²³ Thus the specificity of exercise tests for the diagnosis of important coronary lesions is low in patients with variant angina.

We found that patients with a coronary stenosis of $\geq 75\%$ responded positively to the exercise test without calcium antagonists (sensitivity 100%). In contrast to this Waters *et al*⁷ found that 14 of 36 patients with coronary stenosis of $\geq 70\%$ did not

develop ST segment shifts on exercise testing. They speculated that an inadequate workload was the cause of this large proportion of negative results. It is probable that even in the absence of coronary spasm, ischaemic symptoms or signs will always develop in cases of severe fixed stenosis ($\geq 75\%$) if the patient can complete enough exercise.

Seven of 23 patients with a normal coronary angiogram or mild stenosis developed ST segment changes on exercise. In contrast, seven of eight patients with a moderate coronary stenosis showed a positive response, as did all five patients with severe coronary stenosis. The proportion of patients with positive responses was significantly higher in those with moderate or severe coronary stenoses (12/13, 92%) than in the remainder (7/23, 30%, $p < 0.005$). These results suggest that angina or ST segment shifts develop more easily in patients with moderate coronary stenosis (50–74%) than in those with mild stenoses or none. Larger studies would be needed to confirm this.

Calcium antagonists prevent coronary spasm, and thus pain, in patients with variant angina.^{24–27} They also inhibit exercise induced coronary spasm.^{7–9} A patient taking a calcium antagonist would be expected to have a positive response to exercise only when important coronary stenoses are present, since the false positive response caused by coronary spasm would be abolished.

The results of exercise tests in 57 patients taking calcium antagonists gave a sensitivity of 100% and a specificity of 96% for the diagnosis of coronary stenosis of $\geq 75\%$. Most patients with coronary stenoses of 50–74%, however, had a negative response to the exercise test and the sensitivity of the test was only 48%. An exercise test performed by a patient taking a calcium antagonist may be helpful in the detection of severe coronary stenoses which cause myocardial ischaemia as a result of an increased myocardial oxygen demand, but it cannot detect a moderate coronary stenosis which may cause other coronary events such as thrombotic occlusion.

The specificity of the test will be increased and the false positive response rate reduced by inhibition of the spasm before the exercise test. Spontaneous attacks of variant angina were abolished by calcium antagonists in 55 of 57 patients before the exercise test. Holter monitoring of these patients also confirmed the disappearance of painless ST segment elevation.

ST segment elevation with chest pain developed during tests in four patients taking calcium antagonists. One case had a coronary stenosis of $< 50\%$. It seems most likely that exercise induced the coronary spasm in this patient despite treatment with a cal-

cium antagonist. In the other three patients, who had coronary stenosis of $\geq 75\%$, ST segment elevation may also be an indication of the exercise induced coronary spasm. We do not know whether a higher dose of calcium antagonist would have abolished ST segment elevation in these patients. Exercise can provoke ST segment elevation with chest pain even when doses of calcium antagonists sufficient to abolish the spontaneous attack of variant angina are being taken.

Two patients had one 90 mg dose of diltiazem two hours before the exercise test and we cannot confirm that in these patients the spontaneous attacks were abolished. Both patients showed a true negative response. This single dose was high, but we saw no complications in these two patients or in the 10 patients who were given 90 mg of diltiazem before the test in addition to their daily doses. It would be useful to know whether the administration of a single large dose of calcium antagonist is sufficient to inhibit exercise induced coronary spasm.

Calcium antagonists reduce blood pressure and heart rate to various degrees, and thus they may decrease the pressure-rate product. A decrease in the pressure-rate product by calcium antagonist could have been responsible for the negative response to exercise tests. But the pressure-rate product increased significantly after calcium antagonists in those patients whose positive response to exercise became negative after calcium antagonists. This suggests that calcium antagonists improve the response to exercise not solely through reduction of myocardial oxygen consumption, but also through an improvement in oxygen supply either by inhibition of coronary spasm or by some other mechanism. In patients with severe coronary stenosis, however, the pressure-rate product remained low even after administration of a calcium antagonist. This indicates that in such patients doses of these antagonists that are large enough to inhibit spontaneous attacks of angina do not improve myocardial oxygen supply during exercise.

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Detection of coronary artery disease by thallium scintigraphy in patients with valvar heart disease

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SUMMARY In patients with valvar heart disease detection of coronary artery disease by conventional non-invasive methods may be difficult. The usefulness of thallium-201 exercise scintigraphy for detecting coronary artery disease was evaluated in 16 patients with aortic stenosis, 17 with aortic regurgitation, nine with mitral stenosis, and six with mitral regurgitation who were investigated by coronary angiography. Only two of 21 patients with $\geq 50\%$ coronary artery obstruction had normal thallium images. Three patients without angiographic evidence of coronary artery stenoses had perfusion defects demonstrated by thallium scintigraphy. Only one patient with $\geq 75\%$ coronary stenosis had a normal thallium scan. Angina pectoris or ST segment depression evoked by exercise test were not useful in distinguishing patients with coronary artery disease from those with normal coronary vessels.

These data suggest that thallium exercise scintigraphy may be a useful non-invasive test for detecting coronary artery disease in patients with valvar heart disease.

In patients with valvar heart disease diagnosis of coronary artery disease is difficult without coronary arteriography.¹⁻³ Angina pectoris is an unreliable marker of coronary heart disease, and its absence does not exclude coronary artery disease.¹⁻³ Even exercise electrocardiography does not reliably detect anatomical coronary lesions in patients with valvar heart disease.⁴⁻⁶

Thallium scintigraphy is a sensitive and specific method for detecting angiographically important coronary artery disease,^{6,7} but there is little information on its value in patients with valve diseases.⁸⁻¹⁰ We have assessed the usefulness of thallium scintigraphy in patients with either aortic or mitral valve disease.

Patients and methods

Patients

Forty eight consecutive patients (26 women and 22

men, mean (SD) age 55 (10) years) referred for invasive evaluation of valvar heart disease were studied by thallium exercise scintigraphy and coronary angiography. Beta blocking agents were withdrawn gradually at least 48 hours before the studies. Invasive studies showed aortic stenosis in 16 patients, aortic regurgitation in 17, mitral stenosis in nine, and mitral regurgitation in six. Fifteen patients with aortic valve disease had combined aortic stenosis and regurgitation, and 10 had combined mitral stenosis and regurgitation. Three patients had combined aortic and mitral valve disease. Four patients had mild valvar disease (two with aortic stenosis, one with aortic regurgitation, and one with mitral stenosis), while the others had moderate to severe valve lesions (aortic valve area $< 1.2 \text{ cm}^2$, mitral valve area $< 1.5 \text{ cm}^2$, and 3-4/4 valvar regurgitation in aortography or left ventricular cineangiography). Patients with a history of previous myocardial infarction (two patients) or exertional syncope, inability to perform bicycle ergometer exercise, or congestive heart failure were excluded from the consecutive series. Informed consent was obtained from all the patients.

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CARDIAC CATHETERISATION

All patients underwent left sided cardiac catheterisation, including selective coronary arteriography performed by the Judkins technique. Patients with suspected mitral valve disease also underwent right sided catheterisation. High flow coronary catheters were used in most patients with aortic disease in order to obtain adequate opacification of the coronary arteries. Left ventricular cineangiograms were performed as described elsewhere.¹¹ Cardiac output was determined by the Fick method, and the valve areas were calculated by a modification of Gorlin's formula.¹² The presence and severity of aortic regurgitation were evaluated by aortic root angiography. The angiographic findings were interpreted by two observers who were unaware of the scintigraphic studies. Reduction of $\geq 50\%$ in the luminal diameter of a coronary artery was regarded as an important lesion.

EXERCISE ELECTROCARDIOGRAPHY

A symptom limited exercise test on an electrically braked bicycle ergometer was performed two days before the catheterisation studies. The exercise was started at 30 W and the workload was increased in one minute steps by 15 W for men and 10 W for women. The final workload was the individual maximum determined by the symptoms of angina, dyspnoea, or fatigue. Standard electrocardiographic leads I, aVF, and V5 were monitored.¹³ Cuff blood pressure, heart rate, and ST segment depression were determined every minute up to five minutes after exercise. The electrocardiogram was considered to be positive if more than 0.1 mV ST segment depression was noted during or after the exercise test.

THALLIUM-201 SCINTIGRAPHY

Thallium scintigraphy studies were performed on the day preceding catheterisation by the same exercise protocol that was used for exercise electrocardiography. Thallium-201 (2 mCi (74 MBq)) was injected intravenously 30 to 60 s before completion of the ergometric exercise. Four minutes after the injection imaging was started in the anterior and 45° and 70° left anterior oblique positions with a Siemens Rota-75 gamma camera with a low energy high sensitivity collimator. Post-exercise imaging was completed within 30 min. Scintigraphic imaging was repeated in the same projections four hours after exercise.

Scintigraphic data were collected on a 64 × 64 byte matrix in multigated form for five minutes for each of the views. The images were stored on a Gamma-11 computer disc for analysis. The computer images were enlarged, interpolated, and subjected to back-

ground subtraction.¹⁴ Computer-generated circumferential profiles were obtained from the exercise and delayed images as follows. The myocardium was divided into 36 sectors and radii extending from its centre to its outside contour were constructed by computer. The division into sectors started at 12 o'clock and moved clockwise. The following circumferential curves were calculated from the background subtracted, smoothed images: (a) number of pixels/sector and (b) the normalised counts/pixel. The same regions of interest were used for the post-exercise and delayed images. These curves were displayed on the same image as the normal curves (2 SD) obtained previously.

The scintigrams were interpreted independently by two observers who were not aware of the angiographic findings. Three segments in each view were analysed (anterior, apical, and inferior segment in the anterior projection; posterior, apical, and septal in the 45° left anterior oblique projection; and inferior, apical, and anterior in the 70° left anterior oblique projection). The scintigram was interpreted as indicating coronary artery disease if any area of decreased post-exercise perfusion with or without redistribution in the delayed images was present. An apical defect alone was not considered abnormal, however. Observer agreement was complete in 94% of images. In the remaining 6% (four cases) a consensus was reached with the aid of a third independent observer.

Sensitivity was defined as the number of true positives multiplied by 100 divided by the sum of true positives plus false negatives, specificity as the number of true negatives multiplied by 100 divided by the sum of true negatives plus false positives, and negative predictive accuracy as the number of true negatives multiplied by 100 divided by true negatives plus false negatives.

Results

CLINICAL DATA

Table 1 shows the clinical and exercise data. All the patients had symptoms related to heart disease. Twenty eight had angina pectoris. The sensitivity of angina in predicting the presence of coronary artery disease was 67% (86% for aortic stenosis, 83% for aortic regurgitation, 30% for mitral stenosis, and 100% for mitral regurgitation), and its specificity was 59% (44% for aortic stenosis, 64% for aortic regurgitation, 100% for mitral stenosis, and 60% for mitral regurgitation). The sensitivity of exercise electrocardiography in detecting coronary artery disease was 81% and its specificity was only 52%.

Table 1 Clinical and exercise data (mean (SD))

	Aortic stenosis (n = 16)	Aortic regurgitation (n = 17)	Mitral stenosis (n = 9)	Mitral regurgitation (n = 6)
Age (years)	56 (11)	51 (9)	61 (6)	55 (5)
Sex (males/females)	12/4	8/9	1/8	3/3
New York Heart Association class:				
I or II	4 (25%)	7 (41%)	2 (22%)	3 (50%)
III or IV	12 (75%)	10 (59%)	7 (78%)	3 (50%)
Severity of valve lesion:				
2/4	2 (12%)	1 (6%)	1 (11%)	0
3/4	11 (69%)	11 (65%)	7 (78%)	4 (67%)
4/4	3 (19%)	5 (29%)	1 (11%)	2 (33%)
Occurrence of angina pectoris	12 (75%)	9 (53%)	3 (33%)	2 (33%)
Coronary artery obstructions:				
None	9 (56%)	11 (64%)	2 (22%)	5 (83%)
1 vessel disease	4 (25%)	2 (12%)	2 (22%)	1 (17%)
2 vessel disease	1 (6%)	2 (12%)	3 (34%)	0
3 vessel disease	2 (13%)	2 (12%)	2 (22%)	0
Ergometer exercise data:				
Heart rate _{max} (beats/min)	112 (21)	122 (19)	127 (30)	130 (25)
ST-segment depression	10 (63%)	9 (53%)	5 (56%)	5 (83%)

RELATION BETWEEN SCINTIGRAPHIC DATA AND CORONARY ANGIOGRAPHY

Table 2 shows the occurrence of thallium defects and the presence of angiographically important coronary artery disease in the various groups. Two aortic stenosis patients with angiographically important coronary artery lesions (one with 75% stenosis of the right coronary artery, and the other with 50% stenosis of the left anterior descending coronary artery) had normal scintigraphic images. During exercise neither of these patients reached a heart rate of more than 60% of the age-predicted maximum. Two patients with aortic regurgitation and one with mitral stenosis had abnormal scintigraphy (two patients had fixed anterior defects and one patient had a reversible inferior defect) despite the absence of angiographically important coronary lesions.

When coronary artery stenosis of $\geq 75\%$ was used as the cut-off point, 17 patients had coronary artery disease and only one of these had a normal thallium scan (sensitivity 94%, specificity 90%, and negative

predictive accuracy 97%). Figures 1 and 2 show a true positive scan and a true negative scan. Some of the patients with aortic valve disease had apical perfusion defects, which were not considered to be abnormal.

Discussion

Thallium scintigraphy is a valuable non-invasive method for detecting coronary artery disease,^{6,7} but its usefulness in patients with valvular heart disease has been little studied. Routine cardiac catheterisation could be avoided in some patients with valve disease¹⁵ if coronary artery disease could be assessed non-invasively before valve surgery, and where necessary coronary artery bypass grafting could continue to be done at the same time as valve operation. Our thallium imaging data proved to be reasonably reliable in detecting coronary artery disease in patients with valve lesions; their sensitivity and specificity resembled values obtained in patients without valve lesions.⁶

Table 2 Relation of thallium scintigraphy to presence and absence of coronary artery disease

Coronary artery disease	Number of patients	Normal thallium-201 scintigraphy	One or more thallium-201 defects
Present:			
Aortic stenosis	7	2	5
Aortic regurgitation	6	0	6
Mitral stenosis	7	0	7
Mitral regurgitation	1	0	1
Absent:			
Aortic stenosis	9	9	0
Aortic regurgitation	11	9	2
Mitral stenosis	2	1	1
Mitral regurgitation	5	5	0

Overall sensitivity of thallium scintigraphy, 90%; and specificity, 89%.

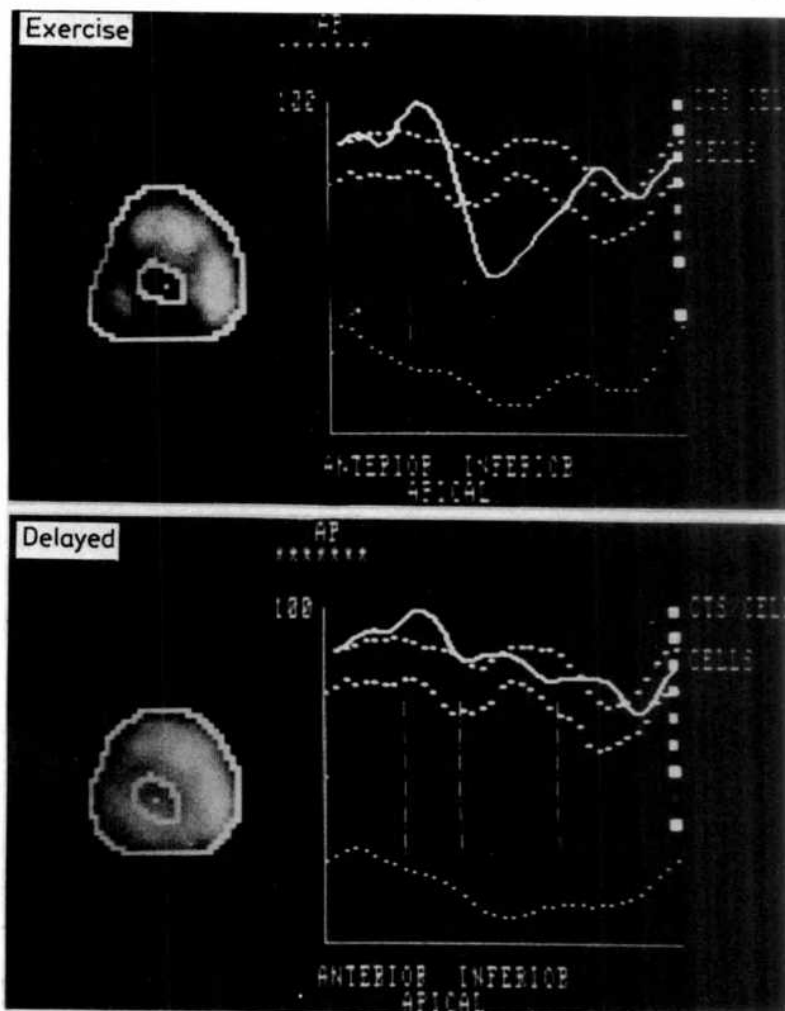


Fig. 1 A thallium scan of a patient with aortic stenosis and stenosis of left anterior descending coronary artery (50%) and right coronary artery (90%). A smoothed, background subtracted, and contrast enhanced thallium image on the left and the corresponding circumferential profile curve on the right (a solid line) show moderately decreased thallium activity of inferoapical segment and a small thallium defect in the anterior segment on the post-exercise image (upper). There is complete redistribution of initial defects on the delayed images (lower). The uppermost dotted line in the profile curve represents normal thallium activity curve, the middle -2 SD from normal, and the lowest dotted line represents the thickness of a left ventricle wall in pixels (CELLS). Counts/pixel (CTS/CELL) in circumferential profile curve are normalised to 100% (solid line). AP, anteroposterior view.

Imaging studies in patients with aortic valve disease have produced conflicting results.^{8,9} Bailey *et al* concluded that qualitative thallium imaging does not allow adequate separation of patients with aortic stenosis and coronary artery disease from those with normal coronary angiography,⁸ whereas, like us,

Pfisterer *et al* found that thallium scintigraphy is reliable for cases of aortic valve disease, provided that apical perfusion defects are not considered to represent coronary artery disease.⁹ Although isotope imaging has been studied in cases of mitral valve prolapse,¹⁵ its usefulness in patients with mitral

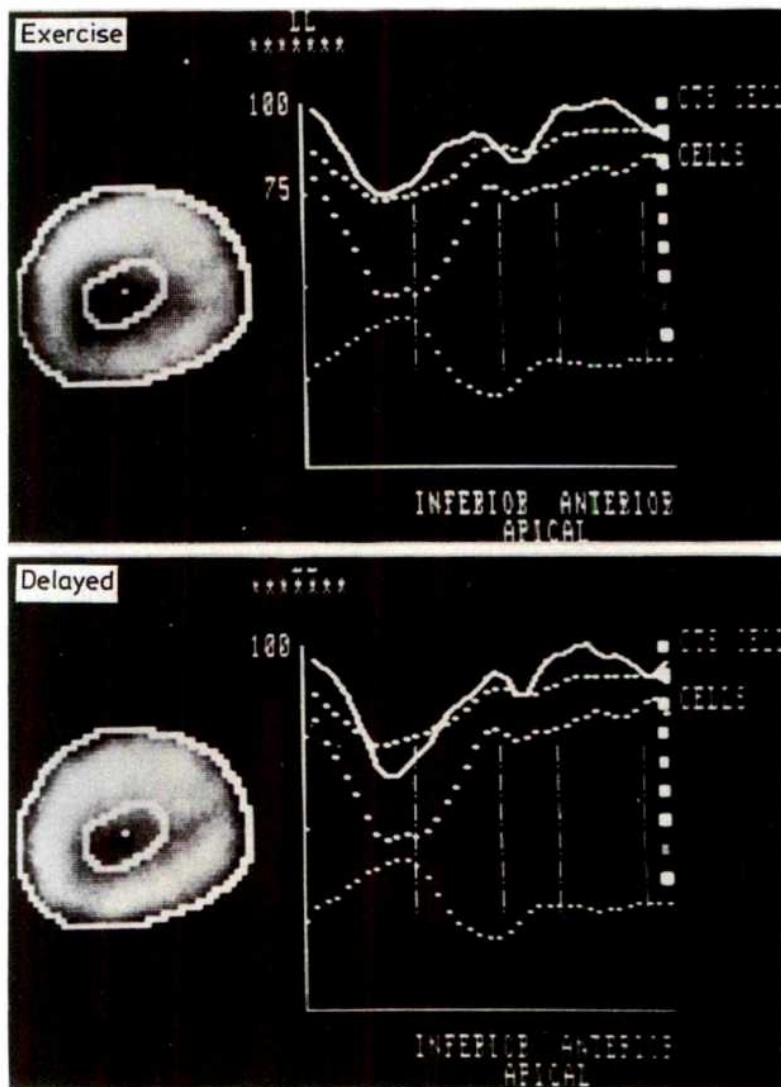


Fig. 2 A thallium scan of a patient with aortic regurgitation and normal coronary angiography. The scintigraphy shows normal thallium activity despite a very slight thinning of apical segment, which was not regarded as abnormal. The uppermost dotted line in the profile curve represents normal thallium activity curve, the middle -2 SD from normal, and the lowest dotted line represents the thickness of a left ventricle wall in pixels (CELLS). Counts/pixel (CTS/CELL) in circumferential profile curve are normalised to 100% (solid lines). LL, left lateral view.

stenosis or regurgitation has not so far been thoroughly examined. Our preliminary data in a small group of patients showed that thallium imaging was quite sensitive and specific in such patients.

Two patients with aortic stenosis had normal thallium scans despite angiographic evidence of coro-

nary artery disease. Both of these patients had low exercise tolerance and they did not reach the acceptable heart rate during exercise. In such cases pharmacological stress testing with dipyridamole might increase the sensitivity of the imaging.¹⁶ As shown by others⁹ apical perfusion defects were quite com-

mon in patients with aortic valve lesions. Apical defects are believed to be a result of alterations in left ventricular geometry without a change in radio-nuclide perfusion.¹⁷

Only one of our patients with $\geq 75\%$ coronary stenosis had a normal thallium scan. Thus in this series thallium imaging was 97% accurate in excluding severe coronary artery disease. The number of patients we studied was small, however, and they do not establish that coronary angiography can be replaced by thallium scintigraphy in patients with valve lesions. Larger studies would allow the analysis of patients by subset (that is type of valve lesion, age, sex, and coronary risk factors), and they should show whether important coronary artery disease can be excluded by non-invasive examination in patients with valvar heart disease.

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Effects of captopril and a combination of hydralazine and isosorbide dinitrate on myocardial sympathetic tone in patients with severe congestive heart failure

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SUMMARY Changes in circulating catecholamines and transmyocardial catecholamine balance associated with improved left ventricular function were studied in patients with chronic heart failure after treatment with captopril (10 patients) and hydralazine in combination with isosorbide dinitrate (eight patients). Cardiac performance improved in response to both captopril and hydralazine-nitrate treatment. The systemic haemodynamic effects were also qualitatively similar, but the hydralazine-nitrate combination caused a greater increase in cardiac index and heart rate. Captopril did not change arterial adrenaline concentrations (0.63 to 0.60 nmol/l), arterial noradrenaline (4.2 to 3.9 nmol/l), or net transmyocardial noradrenaline release (390 to 317 pmol/min), while hydralazine-nitrate increased arterial adrenaline (0.91 to 1.47 nmol/l) and transmyocardial noradrenaline release (225 to 554 pmol/min).

Although both captopril and hydralazine-nitrate treatment improve left ventricular performance in patients with chronic heart failure, hydralazine-nitrate enhances cardiac sympathetic tone and captopril does not. The clinical relevance of these findings, however, is not known.

Captopril and the combination of hydralazine and isosorbide dinitrate are two vasodilator drug regimens which are frequently used to treat patients with congestive heart failure.^{1,2} They have significantly different systemic haemodynamic effects, but the mechanisms for these remain unclear.²⁻⁴ We and others have postulated that these differences may be related to the different effects of these drugs on cardiac sympathetic tone.^{3,5}

In patients with heart failure, captopril has been shown to reduce circulating noradrenaline concentrations,⁶ while the effects of hydralazine have been variable.^{7,8} In order to measure *in vivo* cardiac sympathetic activation it is necessary to measure not only

arterial adrenaline and noradrenaline concentrations but also cardiac catecholamine balance.⁹

We administered captopril or a combination of hydralazine and isosorbide dinitrate to 18 patients with congestive heart failure associated with coronary artery disease. We measured arterial adrenaline, arterial noradrenaline, and transmyocardial catecholamine balance before and after these interventions. Changes in systemic and coronary haemodynamic function were also assessed concurrently.

Patients and methods

Twenty one consecutive patients (16 male and five female) with chronic congestive heart failure associated with coronary artery disease who did not respond to digoxin and diuretic treatment were screened for this study. Three patients were

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excluded—two because of hypertension (mean arterial pressure of 136 and 138 mm Hg), and one patient because of a stroke work index > 35 g/m². The remaining 18 patients enrolled in the study were 46–83 years old and had not experienced an acute ischaemic event for at least three months. In eight of the 18 patients coronary artery disease had been proved by selective coronary arteriography. The other 10 patients had at least one well documented myocardial infarction. Vasodilators were discontinued for 72 hours and all diuretics were discontinued for 24 hours before the start of the study. Digoxin was discontinued for 12 hours before the study.

HAEMODYNAMIC STUDY

Each patient gave informed written consent. The right heart catheterisation was performed with a flow directed balloon tip, and a number 7 Swan-Ganz thermodilution catheter was inserted percutaneously through the right subclavian vein to record right atrial pressure (RAP), pulmonary arterial pressure (PAP), and pulmonary capillary wedge pressure (PCWP). We used the same catheter to measure cardiac output (CO) in triplicate by the thermodilution technique.

Arterial pressure was recorded directly by cannulating the radial artery. The haemodynamic variables were calculated as follows: SVI (ml/beat/m²) = CO/HR/BSA, where SVI is stroke volume index, HR is heart rate, and BSA is body surface area; SWI (g/m²) = SVI $\times$ (MAP – PCWP) $\times$ 0.0136, where SWI is stroke work index, SVI is stroke volume index, MAP is mean arterial pressure, and PCWP is pulmonary capillary wedge pressure; SVR (dyn.s.cm⁻⁵) = (MAP – RAP)/CO $\times$ 80, where SVR is systemic vascular resistance.

Under fluoroscopic guidance, a number 8 thermodilution coronary sinus flow catheter was placed in the coronary sinus through the left subclavian vein. To minimise the coronary sinus reflux¹⁰ the catheter was advanced under fluoroscopy into the mid-coronary sinus. Coronary sinus flow was measured

by the constant infusion thermodilution technique.^{11–13} Coronary sinus flow in ml/min was calculated as [(Tb–Ti)/(Tb–Tm)] $\times$ 1.08 $\times$ 46 ml/min, where Tb is temperature of blood; Ti is temperature of injectate; Tm is temperature of mixture of blood and the injectate; 1.08 is a constant accounting for specific heat and density of both blood and indicator; and 46 ml/min is the injection rate of the indicator (5% dextrose in water) through the Harvard constant infusion pump.

Arterial and coronary sinus blood samples were drawn simultaneously for the determination of oxygen saturation, oxygen content, and lactate, adrenaline, and noradrenaline concentrations. Oxygen saturations were measured in duplicate by a Corning 158 pH and blood gas analyser. Lactate concentrations were measured by the enzymatic fluorometric method of Loomis,¹⁴ adrenaline and noradrenaline concentrations were measured by the radioenzymatic assay of Peuler and Johnson,¹⁵ and the renin concentrations were measured by the New England Nuclear Radioimmunoassay.

Oxygen content was calculated as oxygen saturation $\times$ haemoglobin $\times$ 1.34 and expressed in volume per cent. The arterial – coronary sinus oxygen difference (myocardial oxygen extraction) (ART – CS DO₂) was calculated as arterial oxygen content (ART O₂) – coronary sinus oxygen content (CS O₂). Myocardial oxygen consumption (MVO₂) was calculated as (ART – CS DO₂) $\times$ CSF (ml/min) $\times$ 10, and is expressed as ml of O₂ per min, where CSF is coronary sinus flow. Myocardial lactate extraction was calculated as (ART lactate – CS lactate)/(ART lactate) $\times$ 100, where ART lactate is arterial lactate concentration (mg/100 ml) and CS lactate is coronary sinus lactate concentrations. Transmyocardial noradrenaline values (pmol/min) were calculated as (coronary sinus noradrenaline – arterial noradrenaline) $\times$ coronary sinus blood flow (ml/min).

DRUG DOSAGE

Once the catheters were inserted, the first 10 patients received captopril in increasing doses (6.25, 12.5, 25,

Table 1 Changes in systemic haemodynamic function (mean (SD))

	Heart rate (beats/min)	Mean blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	PCWP (mm Hg)	Cardiac index (l/min/m ²)	Stroke work index (g m/m ²)	SVR (dyn s cm ⁻⁵)
Captopril:							
Baseline	94 (18)	92 (6)	72 (6)	26 (11)	2.1 (0.8)	21 (8)	1913 (627)
Peak	92 (19)	79 (11)†	61 (10)†	21 (8)*	2.3 (0.8)*	19 (5)	1459 (470)†
Hydralazine + isosorbide dinitrate:							
Baseline	100 (11)	93 (16)	71 (5)	27 (6)	1.8 (0.3)	17 (9)	2031 (470)
Peak	107 (12)*	77 (15)†	57 (12)*	21 (10)*	2.5 (0.3)†	17 (5)	1273 (505)*

*p < 0.05 vs control; †p < 0.01 vs control.

PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

50, 100, 150, and 200 mg) every hour (mean 180 mg, but seven of 10 patients responded at doses < 100 mg) until there was a > 10 mmHg decrease in mean arterial pressure, or the second dose of 200 mg of captopril was given.³ At this time a complete set of measurements was repeated. The next eight patients received a single 100 mg dose of hydralazine and, 90 min later, received 30 mg of oral isosorbide dinitrate. After another 30 min (120 min after the

original hydralazine dose) a complete set of measurements was repeated.³

STATISTICAL ANALYSIS

The effect of a vasodilator in any given patient was compared with baseline values by a two tailed paired t test. The change in any given variable caused by captopril was compared with that caused by the hydralazine-nitrate combination by a two tailed,

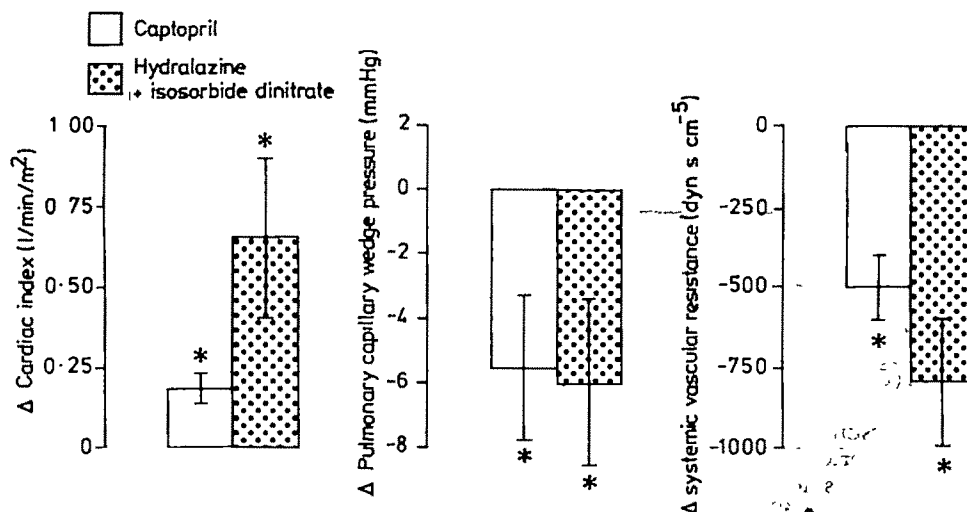


Fig 1 Systemic haemodynamic effects of captopril and hydralazine + isosorbide dinitrate in patients with severe congestive heart failure. Cardiac index increased in both groups of patients but the magnitude of increase was significantly greater in patients treated with hydralazine + isosorbide dinitrate. In both groups pulmonary capillary wedge pressure and systemic vascular resistance decreased to a similar extent. Δ, change from control; * $p < 0.05$ vs control. Values are mean (SE).

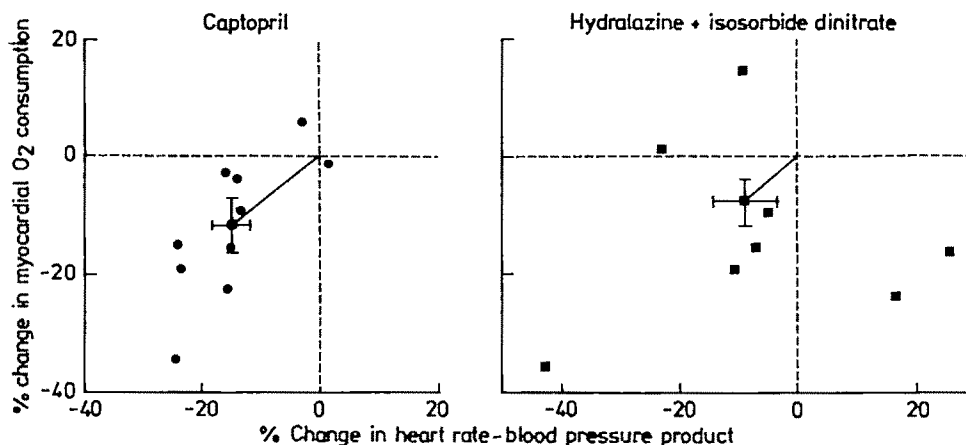


Fig 2 Relation between the percentage change in rate-pressure product and percentage change in myocardial oxygen consumption with captopril and with hydralazine + isosorbide dinitrate. The decrease in myocardial oxygen consumption with captopril parallels the decrease in the rate-pressure product, $r = 0.81$, whereas this relation varies with hydralazine + isosorbide dinitrate. Values for mean (SE) are shown.

Table 2 Changes in coronary haemodynamic function (mean (SD))

	HR × BP (mm Hg/min × 10 ⁻³)	CSF (ml/min)	ART - CS DO ₂ (vol %)	MVO ₂ (ml/min)	Lact extr (%)
Captopril:					
Baseline	12.7 (2.6)	126 (45)	9.8 (1.4)	11.0 (5.1)	4 (18)
Peak	10.9 (2.5)†	111 (39)*	9.6 (1.1)	9.6 (4.5)†	7 (9)
Hydralazine + isosorbide dinitrate:					
Baseline	14.1 (2.7)	106 (59)	10.1 (1.1)	9.9 (6.2)	18 (25)
Peak	12.7 (2.8)	94 (41)	9.0 (1.4)*	8.8 (4.0)	6 (26)

*p < 0.05 vs control; †p < 0.01 vs control.

HR × BP, rate-pressure product; CSF, coronary sinus blood flow; ART - CS DO₂, myocardial oxygen extraction; MVO₂, myocardial oxygen consumption; Lact extr, myocardial lactate extraction.

Table 3 Changes in myocardial sympathetic tone (mean (SD))

	Arterial noradrenaline (nmol/l)	Coronary sinus noradrenaline (nmol/l)	Transmyocardial noradrenaline (pmol/min)	Arterial adrenaline (nmol/l)
Captopril:				
Baseline	4.2 (3.1)	7.0 (4.6)	390 (593)	0.63 (0.65)
Drug	3.9 (1.9)	6.3 (3.6)	317 (415)	0.60 (0.34)
Hydralazine + isosorbide dinitrate:				
Baseline	6.7 (5.7)	8.7 (8.2)	225 (484)	0.91 (0.58)
Drug	7.5 (7.3)	12.0 (11.4)*	554 (522)*	1.47 (0.75)†

*p < 0.05; †p < 0.01.

unpaired t test. All values are mean (SD) unless otherwise specified.

Results

SYSTEMIC HAEMODYNAMIC FUNCTION

Baseline systemic haemodynamic function in both

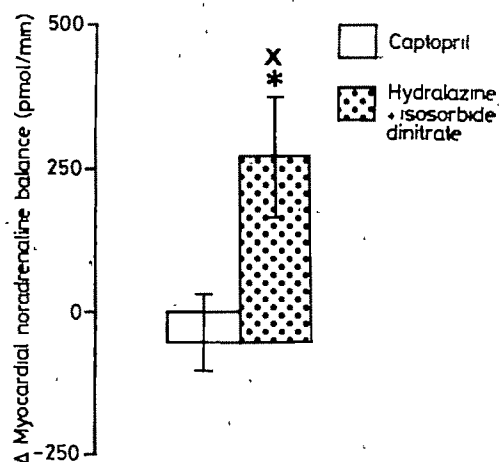


Fig 3 Effects of captopril and hydralazine + isosorbide dinitrate on net cardiac noradrenaline balance. There was no change in cardiac noradrenaline release with captopril, whereas hydralazine + isosorbide dinitrate increased net myocardial noradrenaline release compared with control or captopril. Myocardial noradrenaline balance = coronary sinus - arterial noradrenaline concentration × coronary sinus flow. Values for mean (SE) are shown. *p < 0.05 vs control, × p < 0.05 vs captopril.

groups was similar (table 1). Captopril and the hydralazine-nitrate decreased systemic arterial pressure and pulmonary capillary wedge pressure to a similar extent; however, hydralazine-nitrate caused a larger increase in cardiac index and stroke volume index than did captopril (table 1, fig 1). Only hydralazine-nitrate caused a statistically significant increase in heart rate.

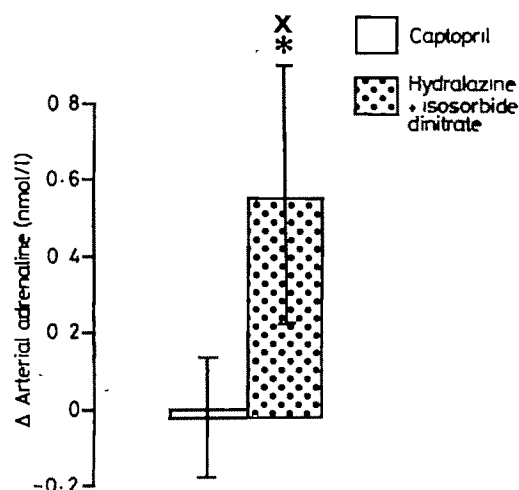


Fig 4 Change in arterial adrenaline concentration with captopril and hydralazine + isosorbide dinitrate. Hydralazine + isosorbide dinitrate increased arterial adrenaline whereas captopril had no effect. *p < 0.05 vs control, × p < 0.05 vs captopril.

CORONARY HAEMODYNAMIC FUNCTION

Captopril reduced the rate-pressure product, coronary sinus blood flow, and global myocardial oxygen consumption (table 2, fig 2). Hydralazine-nitrate also tended to decrease the rate-pressure product, coronary sinus flow, and average myocardial oxygen consumption, but the changes were variable (table 2, fig 2) and not statistically significant ($p > 0.1$). Global myocardial lactate extraction did not change in either group.

MYOCARDIAL SYMPATHETIC ACTIVATION

Captopril had no effect on arterial catecholamines or on transmyocardial catecholamine balance, whereas the combination of hydralazine-nitrate increased both arterial adrenaline and net transmyocardial noradrenaline release (table 3, figs 3 and 4). The increase in transmyocardial noradrenaline release with the combination of hydralazine and isosorbide dinitrate was primarily due to an increase in coronary sinus noradrenaline concentrations.

Discussion

This study confirms the differences in the short term systemic and coronary haemodynamic effects of captopril and the combination of hydralazine-isosorbide dinitrate in patients with chronic heart failure.^{1,2} Hydralazine-nitrate increases heart rate and cardiac index more than captopril does. With captopril the rate-pressure product fell consistently and myocardial oxygen requirements were reduced. There was a predictable decrease in myocardial oxygen consumption. With hydralazine-nitrate,^{2,3} however, no such relation was observed. The precise mechanism for these differences remains unclear; however, a reflex increase in myocardial sympathetic activation with hydralazine-nitrate that was not seen with captopril may provide a possible explanation.

This study demonstrated considerable differences in the short term effects of hydralazine-nitrates and captopril on circulating catecholamines and on transmyocardial catecholamine balance. With hydralazine-nitrate, arterial adrenaline increased and there was also a tendency for noradrenaline concentrations to be higher. Furthermore, the net transmyocardial release of noradrenaline increased in response to hydralazine-nitrate. With captopril, although the changes in circulating catecholamines and in transmyocardial catecholamine balance were not statistically significant, there was a tendency to lower arterial noradrenaline concentrations and decreased net transmyocardial noradrenaline release.

Because neither hydralazine nor isosorbide dinitrate has any direct effect on the sympathetic system,¹⁶⁻¹⁸ it is probable that the difference between

these two regimens is the result of a direct neurohumoral effect of captopril on the sympathetic system.¹⁹⁻²¹ Converting enzyme inhibition reduces sympathetic activity in heart failure by attenuating the effects of angiotensin. Both hydralazine-nitrate and captopril reduced systemic arterial pressure; thus reflex activation of the sympathetic system should occur in response to both. It is likely, therefore, that captopril exerted a deactivating balancing influence on the sympathetic system, which probably resulted from its direct neurohumoral effect. With hydralazine-nitrate, reflex sympathetic activation remained unopposed. The observed differences in systemic and cardiac sympathetic activity in response to hydralazine-nitrate and captopril may have clinical relevance. The increase in heart rate and greater increase in stroke volume after hydralazine-nitrate may result from the reflex increase in sympathetic tone and contractility.

It has been suggested that an increase in the activity of circulating noradrenaline is associated with worse prognosis.²² It is possible, therefore, that the increase in cardiac sympathetic tone caused by the hydralazine-nitrate might have deleterious effects. Furthermore, an increase in sympathetic tone may activate the renin-angiotensin-aldosterone system and thus promote salt and water retention.

The mechanism by which captopril prevents cardiac sympathetic activation remains speculative; it is probably the result of attenuation of angiotensin II activity. Angiotensin II enhances sympathetic tone by central and peripheral mechanisms,¹⁹⁻²¹ and angiotensin II converting enzyme inhibitors have been shown to decrease hypoxia mediated noradrenaline release²³ and to decrease the circulating catecholamines in hypertensive patients.²⁴

This study has several limitations. First of all, these measurements were done with the patient in the supine position and there may be important differences between measurements taken while the patient is lying or standing.²⁵ Second, coronary sinus blood flow determinations do not allow assessment of changes in regional blood flow, and important differences in perfusion are likely to occur in the presence of coronary artery disease. Nevertheless, this study shows that there are important differences between the effects of captopril and hydralazine-nitrate on cardiac sympathetic tone, despite their similar haemodynamic effects. Further studies will be required to evaluate the clinical relevance of these findings.

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Reliability of non-invasive estimates of pulmonary hypertension by pulsed Doppler echocardiography

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SUMMARY The duration of the acceleration phase of pulmonary systolic flow was measured by pulsed Doppler echocardiography in 39 normal subjects and 67 patients with heart disease to evaluate the reliability of this Doppler index as an estimate of pulmonary arterial pressure. The mean (SD) Doppler index in patients with abnormal mean pulmonary arterial pressure (> 15 mm Hg) was significantly shorter than that in normal subjects (110 (30) ms vs 150 (10) ms). The Doppler index was significantly related to the mean pulmonary arterial pressure ($r = -0.75$) the pulmonary blood flow ($r = 0.46$), and the total pulmonary vascular resistance ($r = -0.68$). Forty four of 45 patients with an abnormal index (≤ 120 ms) showed abnormal mean pressure (> 15 mm Hg). Without exception patients with a low index (≤ 90 ms) had distinct pulmonary hypertension (≥ 25 mm Hg). Twelve of 22 patients with a normal index (≥ 130 ms), however, also showed abnormal pressures. Nine of the 12 had an atrial septal defect and they had high pulmonary arterial pressure associated with high blood flow. Eighteen patients with valvar heart disease, whose mean pulmonary arterial pressure ranged from 16 mm Hg to 24 mm Hg, had a significantly shorter acceleration phase and a higher total vascular resistance than 11 patients with atrial septal defect in whom the pressure range was similar (120 (20) ms vs 140 (20) ms, 3.8 (1.1) hybrid resistance unit vs 1.6 (0.5)).

Thus although the acceleration time of the pulmonary systolic flow is useful for the evaluation of pulmonary hypertension, it is a complex index that is affected not only by pulmonary arterial pressure but also by pulmonary blood flow and pathological changes in the pulmonary vascular bed.

Abnormal systolic flow patterns in the pulmonary artery and in the right ventricular outflow tract in patients with pulmonary hypertension have been detected in experimental studies by electromagnetic measurement of flow,¹ and by clinical studies with Doppler echocardiography²⁻⁵ and contrast echocardiography.⁶ In pulmonary hypertension the pulmonary systolic flow begins to decelerate prematurely,²⁻⁵ with or without a subsequent re-acceleration in late systole.^{3,5} The initial acceleration phase of the systolic flow velocity curve in

patients with pulmonary hypertension is characteristically shorter than that in normal subjects,⁴ and the duration of the acceleration phase decreases as the pulmonary hypertension progresses.^{4,5} This Doppler index may provide a non-invasive method for the evaluation of pulmonary arterial pressure. Pulmonary arterial pressure, however, depends on pulmonary flow volume and pulmonary vascular impedance. The duration of the acceleration phase in a patient with high flow volume may be different from that in another patient with high peripheral resistance, even if pulmonary arterial pressure is the same in both patients. Furthermore, right ventricular contractility may affect the pulmonary systolic flow pattern.

We have studied the relation between the duration of the acceleration phase of pulmonary systolic flow and haemodynamic variables in various diseases to

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evaluate the reliability of this Doppler index as an estimate of pulmonary arterial pressure.

Patients and methods

The study groups consisted of 39 control patients (17 men and 22 women; age range 20–48), 67 patients with heart disease (32 men and 35 women; age range 19–67) who underwent cardiac catheterisation, and three additional patients (two men and one woman; aged 28, 62, and 41) with severe right ventricular dysfunction (two had Uhl's anomaly and one had arrhythmogenic right ventricular dysplasia). Forty one of the 67 patients had valvar heart disease; 14 had an atrial septal defect, eight had ischaemic heart disease, three had primary pulmonary hypertension, and one had progressive systemic sclerosis.

Right heart catheterisation was performed within 1–6 days of pulsed Doppler echocardiographic investigation in the 70 patients with heart disease. Pulmonary arterial pressure (PAP) was measured by means of a fluid filled catheter and a pressure transducer (Electronics for Medicine). Pressure tracings were recorded on a recorder (Electronics for Medicine) at 50 mm/s paper speed. Pulmonary blood flow volume (PBF) was obtained by the Fick method. Total pulmonary vascular resistance was calculated as $PBF \div \text{mean PAP}$. All patients were clinically stable, and none showed overt signs of congestive heart failure during the study.

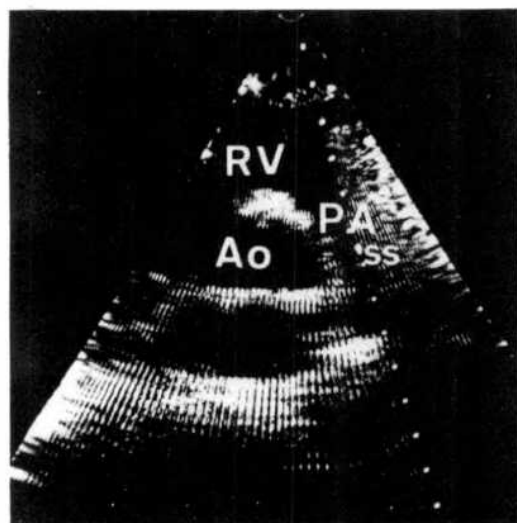


Fig 1 Sampling site of the Doppler signal. The pulmonary flow velocity curve was recorded at the root of the main pulmonary artery. RV, right ventricle; PA, pulmonary artery; Ao, aorta; ss, sampling site.

Pulsed Doppler echocardiograms were obtained with an ultrasonic pulsed Doppler unit combined with a cross sectional and an M mode echocardiograph (Toshiba, or Aloka). The instruments have a 2.4 MHz phased array transducer (Toshiba) and a 2.75 MHz mechanical transducer (Aloka). After the sampling site of the Doppler signal had been established on the cross sectional image, the system was used in the Doppler mode (pulse repetition rates 6 KHz (Toshiba) and 4.4 KHz (Aloka)). Doppler output was obtained as spectral display by fast Fourier transformation. The bidirectional Doppler signal was recorded simultaneously with M mode echocardiogram, phonocardiogram, and electrocardiogram on a strip chart recorder (Honeywell) at a 50 mm/s paper speed. The examinations were performed with the patient supine and the transducer on the parasternal area. The sampling site for Doppler echocardiography was positioned distal to the pulmonary valve leaflets in the main pulmonary artery (fig 1). The width of the sampling volume along the ultrasonic beam was 2 mm. Kitabatake *et al* preferred to measure the flow in the right ventricular outflow tract rather than the pulmonary arterial flow, because the Doppler signals from the flow obtained in the latter position were often affected by a mixing of signals caused by systolic fluttering of the pulmonary valve cusp, by eddy currents in patients with pulmonary hypertension, or by both.⁵ We, however, were able to record flow velocity curves more clearly in the pulmonary artery than in the right ventricular outflow tract, when the sampling site was located in the middle of the pulmonary trunk distal to the pulmonary valve.

Doppler velocity flow curves showed that systolic ejection flow was away from the transducer, that is

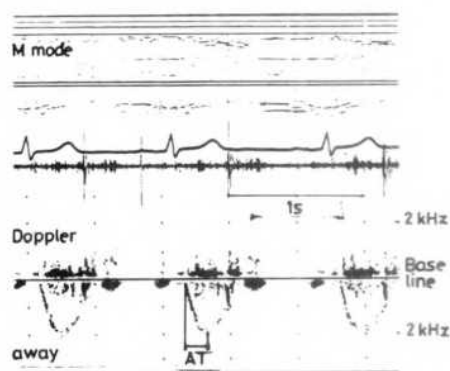


Fig 2 Pulmonary flow velocity curve in a normal subject. The course of ejection flow velocity is shown as a monophasic curve peaking in mid-systole and sustained to end systole. The acceleration time (AT) was measured from the onset of ejection to the peak flow velocity.

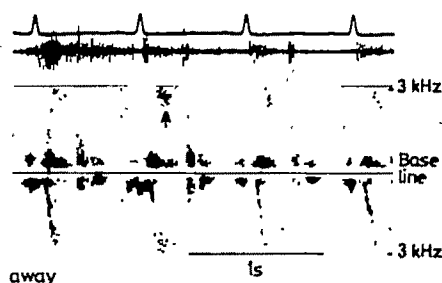


Fig 3 Flow velocity curve in a patient with high flow velocity. When flow velocity exceeded the maximum detectable velocity of the pulsed Doppler method, the aliased Doppler signal (arrow) is displayed on the opposite side of the baseline. The time of the peak flow was determined from this aliased signal.

from the right ventricular outflow tract into the main pulmonary artery (fig 2). The duration of the acceleration phase of ejection flow (acceleration time) was measured from the onset of ejection to the peak flow velocity, as shown in fig 2. Acceleration time was averaged over ten consecutive cardiac cycles. When flow velocity exceeded the maximum detectable velocity, which depends on the ultrasonic pulse repetition rate, the aliased Doppler signal was displayed above the base line as shown in fig 3. In most of these cases the time of peak flow could be determined from the aliased signal. In seven patients with atrial septal defect, however, the peak flow could not be measured exactly. In these patients we used the flow velocity curve of the right ventricular outflow tract to measure acceleration time. The difference between the acceleration time value at the pulmonary artery and that at the right ventricular outflow tract was calculated by comparison of these values in 14 patients (nine patients with valvar heart disease and five with atrial septal defect).

Kitabatake *et al* used the ratio of acceleration time to right ventricular ejection time to evaluate pulmonary hypertension.⁵ We, however, were not always able to determine exactly the end point of right ventricular ejection if the late systolic part of the flow curve showed a stationary or backward flow pattern. Moreover, there was more beat to beat variation in ejection time than in acceleration time, especially in patients with atrial fibrillation (fig 4b). Thus we did not use right ventricular ejection time.

Data were analysed by the *t* test for comparison of means between the two groups. Relations between variables were analysed by linear regression. The significance of difference between correlation coefficients was tested by Fisher's Z transformation of the coefficients. The level of significance was set at $p < 0.05$.

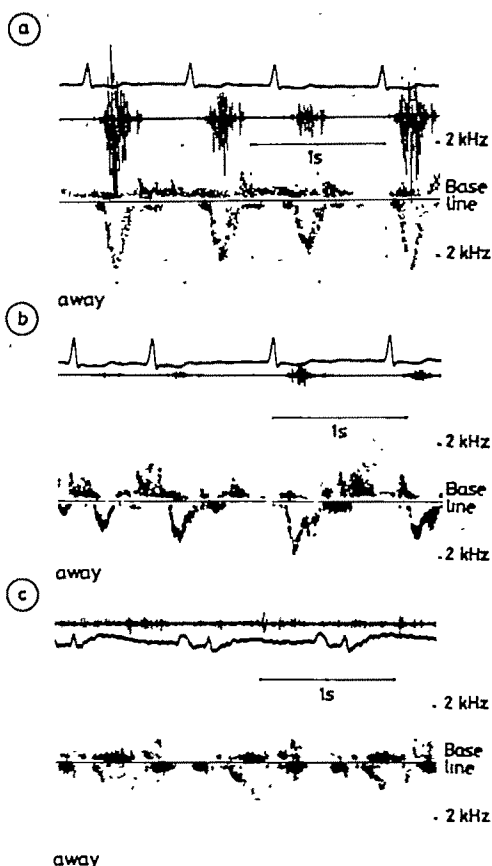


Fig 4 Flow velocity curves in patients with various heart diseases (a) In pulmonary hypertension the peak of the flow appeared prematurely and was followed by a sharp fall in flow velocity. In atrial fibrillation (b) the late systolic part of the flow curve changed from beat to beat. There was re-acceleration of flow in the third and the fourth cycles. In the first beat there was no flow or reversed flow in the right ventricular outflow tract. In a patient with a weakly contracting right ventricle (c) the course of the flow curve resembled the normal flow pattern; however, the velocity reached a peak in late systole.

Results

The systolic flow velocity curve in normal patients started at the beginning of systole and was sustained to the end of systole, peaking in mid-systole (fig 2). In most patients with pulmonary hypertension, the peak of the flow velocity appeared prematurely, and there was a sharp decrease in flow velocity in mid-systole (fig 4a). The later part of the systolic curves showed two characteristic kinds of pattern, a re-accelerated flow that produced a second peak and a neutral or sometimes reversed flow (fig 4b). One of

Table 1 Acceleration time (mean (SD)) measured in the pulmonary artery and in the right ventricular outflow tract

	Patient no	AT (ms)		p
		PA	RVOFT	
VHD	9	110 (20)	110 (20)	NS
ASD	5	130 (40)	140 (40)	NS

AT, acceleration time of pulmonary ejection flow; PA, pulmonary artery; RVOFT, right ventricular outflow tract; VHD, valvar heart disease; ASD, atrial septal defect.

the patterns was observed for individual patients or for different beats in patients with atrial fibrillation. The course of the ejection flow curve in patients with impaired contraction of the right ventricle resembled the normal flow pattern, though the flow velocity peaked in late systole (fig 4c).

There were no significant differences between the acceleration time determined at the pulmonary artery and that determined at the right ventricular outflow tract (table 1). The mean (SD) acceleration time in control subjects was 150 (10) ms with a range

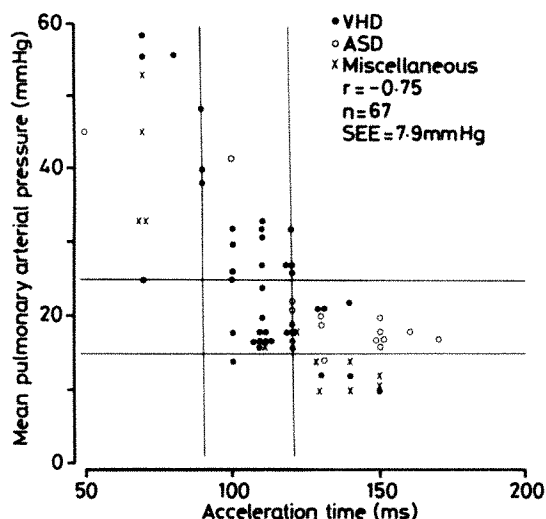


Fig 5 Relation between acceleration time (AT) and mean pulmonary arterial pressure (mPAP) in patients with various heart diseases. The acceleration time decreased with an increase in pulmonary arterial pressure. The linear regression equation was $mPAP = 65 - 0.35AT$ and the F value was 86 ($F(0.05\%) = 3.9$). Ten of 11 patients with normal pressure (< 15 mm Hg) showed a normal AT (≥ 130 ms). All 25 patients with mean pressure > 25 mm Hg had an abnormal value (< 120 ms). Patients with an extremely short AT (≤ 90 ms) had distinct pulmonary hypertension (≥ 25 mm Hg). Twelve of 22 patients with a normal AT, however, had abnormal pulmonary artery pressure. Nine of these 12 subjects had atrial septal defect (ASD). VHD, valvar heart disease.

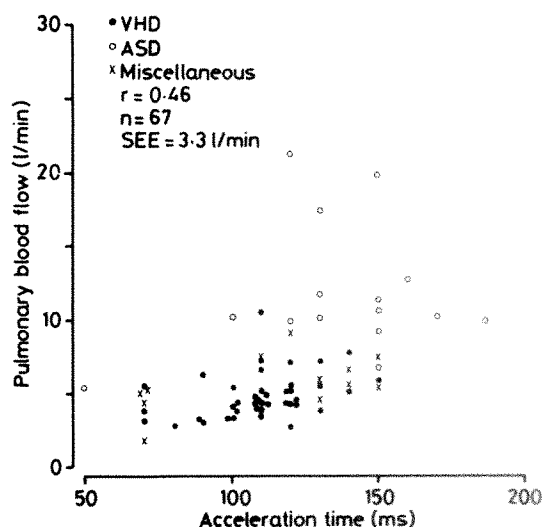


Fig 6 Relation between acceleration time (AT) and pulmonary blood flow (PBF). The linear regression equation was $PBF = -1.4 + 0.069AT$ and the F value was 18. Most patients with atrial septal defect (ASD) had a long AT and high blood flow volume. VHD, valvar heart disease.

from 130 ms to 180 ms. The acceleration time in those with heart disease ranged from 50 ms to 170 ms (110 (30) ms), and was inversely related to mean pulmonary arterial pressure ($r = -0.75$, $p < 0.001$ (fig 5)).

The acceleration time was significantly shorter in patients with an abnormal mean pulmonary arterial pressure (> 15 mm Hg⁷) than in patients without heart disease (110 (30) ms, $p < 0.001$). When abnormal acceleration time was defined as being < 120 ms (according to the range of the values in the controls), 44 of 45 patients with an abnormal index had an abnormal mean pulmonary arterial pressure. All 25 patients whose mean pulmonary arterial pressure was > 25 mm Hg had an abnormal acceleration time. All 12 patients in whom acceleration time was < 90 ms had definite pulmonary hypertension (mean pulmonary arterial pressure ≥ 25 mm Hg). Ten of 11 patients with a normal pulmonary arterial pressure had a normal acceleration time. Twelve of 31 patients, however, whose mean pulmonary arterial pressure ranged from 16 mm Hg to 24 mm Hg had a normal acceleration time. Twelve of the 22 patients with normal acceleration time (≥ 130 ms) showed abnormal mean pulmonary arterial pressure (> 15 mm Hg). Nine of these 12 subjects had atrial septal defect.

Acceleration time also correlated with the pulmonary blood flow volume ($r = 0.46$, $p < 0.001$ (fig 6)), and the total pulmonary vascular resistance

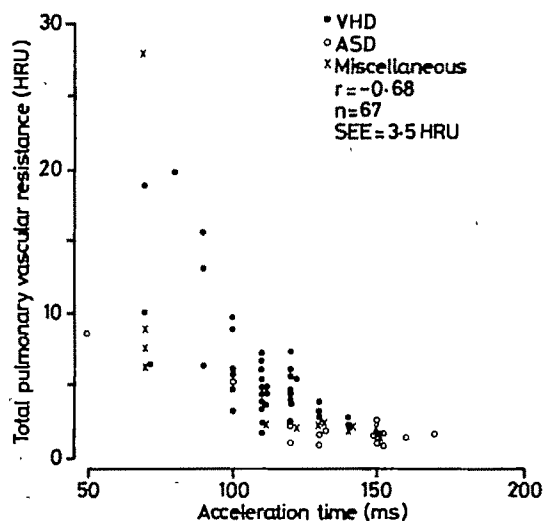


Fig 7 Relation between acceleration time (AT) and total pulmonary vascular resistance (TPR). The linear regression equation was $TPR = 2.0 - 0.13AT$ and the *F* value was 57. Patients with atrial septal defect (ASD) who had long acceleration time had low vascular resistance. VHD, valvar heart disease.

($r = -0.68$, $p < 0.001$ (fig 7)). The correlation between acceleration time and pulmonary blood flow was not as strong as that between acceleration time and mean pulmonary arterial pressure ($p < 0.001$). Patients with atrial septal defect, whose pulmonary blood flow volume was generally high, tended to have longer acceleration times (fig 6). The correlation coefficient between acceleration time and total pulmonary vascular resistance was not significantly different from that between acceleration time and mean pulmonary arterial pressure. The total pulmonary vascular resistance in patients with atrial septal defect with a normal acceleration time, however, tended to be low (fig 7).

Relations between acceleration time and haemodynamic function appeared to be curvilinear (fig 5 and fig 7). When acceleration time was compared with $\log_{10}$ mean pulmonary arterial pressure (mPAP) and $\log_{10}$ total pulmonary vascular resistance (TPR), the correlation coefficients were

Matsuda, Sekiguchi, Sugishita, Kuwako, Iida, Ito

-0.75 and -0.79 respectively. Again there was no significant difference between these correlation coefficients. The regression equations for these relations were $\log_{10} (mPAP) = 2.0 - 0.0057AT$ (*F* value = 83, *SEE* = 0.13), and $\log_{10} (TPR) = 1.8 - 0.010AT$ (*F* value = 108, *SEE* = 0.21) respectively, where AT is acceleration time and *SEE* is standard error of estimate.

The acceleration time in 11 patients with atrial septal defect in whom mean pulmonary arterial pressure ranged from 16 mm Hg to 24 mm Hg was significantly longer than that in 18 patients with valve disease in whom the range of mean pulmonary arterial pressures was similar (19 (2) mm Hg *vs* 19 (2) mm Hg, NS; acceleration time (140 (20) ms *vs* 120 (10) ms, $p < 0.005$). The same patients with atrial septal defect had significantly lower total pulmonary vascular resistance than patients with valve disease (1.6 (0.5) HRU *vs* 3.8 (1.1) HRU, $p < 0.001$). Patients with atrial septal defect in whom total pulmonary vascular resistance was increased and in whom pulmonary hypertension was severe had an abnormal acceleration time, however (fig 5 and fig 7). The correlation coefficient between acceleration time and mean pulmonary arterial pressure in patients with atrial septal defect was -0.87 ; in the remainder it was -0.78 . The regression equation for acceleration time (AT) in patients with atrial septal defect was $mPAP = 57 - 0.27AT$ (*F* value = 36, standard error of estimate = 4.8 mm Hg) and that in the other patients was $mPAP = 74 - 0.44AT$ (*F* value = 78, *SEE* = 8.0 mm Hg).

In the three patients with severe right ventricular dysfunction the acceleration time was longer than normal (160–230 ms, table 2). We did not apply statistical tests to this small group. Right ventricular angiography showed a dilated right ventricle with poor systolic function and tricuspid regurgitation. There was a slight increase in mean pulmonary arterial pressure and total pulmonary vascular resistance, which we think is caused by a rise in pulmonary capillary pressure (table 2).

Discussion

The acceleration time of pulmonary arterial systolic

Table 2 Acceleration time and haemodynamic data in patients with severe right ventricular dysfunction

Patient No	AT (ms)	Mean PAP (mm Hg)	PBF (l/min)	TPR (HRU)	Mean PC (mm Hg)
1	160	17	4.5	3.8	15
2	230	14	3.9	3.6	—
3	230	16	—	—	12

AT, acceleration time; mean PAP, mean pulmonary arterial pressure; PBF, pulmonary blood flow; TPR, total peripheral vascular resistance; mean PC, mean pulmonary capillary pressure

flow, measured by Doppler echocardiography, decreased with an increase in pulmonary arterial pressure. The correlation coefficient obtained in this study ($r = -0.75$) resembled that reported by Kitabatake *et al* ($r = -0.82$).⁵ Most patients with an abnormal index had abnormal pulmonary arterial pressure. Without exception, patients with an extremely short acceleration time (≤ 90 ms) had prominent pulmonary hypertension. In all patients with pulmonary hypertension the acceleration time was abnormal, and in most patients with normal pulmonary arterial pressure it was normal. Thus echocardiographic measurement of the acceleration phase of pulmonary arterial ejection flow at first appeared to be a promising non-invasive index of pulmonary hypertension.

In 12 of 22 patients with a normal index, however, pulmonary arterial pressure was abnormal (that is the mean pressure was >15 mm Hg and <25 mm Hg). Nine of these 12 patients had an atrial septal defect. In this study pulmonary blood flow was high in most patients with atrial septal defect. The acceleration time of ejection flow correlated not only with pulmonary arterial pressure, but also with pulmonary blood flow volume, that is the acceleration time increased with an increase in blood flow volume. Patients with an atrial septal defect and a normal Doppler index tended to have high pulmonary pressures associated with high blood flow volumes. Pulmonary vascular resistance was low in these patients. In contrast, the acceleration time was shorter than normal in patients with valvar heart disease, who had comparable pulmonary arterial pressure and higher peripheral resistance. The Doppler index was abnormal even in patients with atrial septal defect when pulmonary vascular resistance was increased. These results suggest that the duration of the acceleration phase of pulmonary systolic flow is more strongly influenced by pathological changes in the pulmonary vascular bed than by pulmonary arterial pressure itself.

The premature deceleration of pulmonary systolic flow in patients with pulmonary hypertension indicates that the pressure gradient between the right ventricular outflow tract and the pulmonary artery is reversed and counteracts systolic flow earlier than usual. In an earlier study we proposed two mechanisms to explain this early reversal of the pressure gradient in patients with pulmonary hypertension³: that decreased distensibility of the vessel wall⁶ may increase the amplitude of the pressure wave propagated from the right ventricular outflow tract into the pulmonary trunk; and that the reflection of the pressure wave at the peripheral vascular bed is increased by reduced vessel calibre or obstruction of the pulmonary arterioles and capillaries, so that the

reflected wave front reaches the pulmonary trunk prematurely through the stiffened vessels in such patients. These two mechanisms would result in an earlier reversal of the pressure gradient, that in turn would produce earlier deceleration of pulmonary systolic flow.

Our results are compatible with the finding reported by Milnor *et al* that pressure wave velocity was highest in the subjects with the highest pulmonary vascular resistance at any given mean pressure.⁹ They suggested that the increases in pulmonary arterial pulse wave velocity and impedance in their patients were not entirely due to passive distension of the artery by high transmural pressure, and that the pathological stiffening of the larger arteries in patients with high vascular resistance was greater than that produced by an uncomplicated increase in distending pressure. Patients with high pulmonary vascular resistance are likely to have histological alterations both in the peripheral vascular bed and in the large arteries; these will cause higher pressure peaks, a higher flow velocity, and a larger reflection of the pressure pulse wave. All of these effects will result in an earlier deceleration of pulmonary systolic flow than in patients with low pulmonary vascular resistance.

The acceleration phase of pulmonary systolic flow was prolonged in three patients with severe right ventricular dysfunction. Mean pulmonary arterial pressure and total peripheral vascular resistance were slightly increased. The increase may have resulted from raised pulmonary venous pressure rather than histological changes in the pulmonary arteries. Impaired ventricular contraction alone might not cause an early deceleration of pulmonary systolic flow if the pulmonary vascular bed is normal. In these three patients right ventricular angiography showed pronounced tricuspid regurgitation. Kitabatake *et al* reported that the good correlation between the Doppler acceleration index and mean pulmonary arterial pressure held irrespective of underlying tricuspid regurgitation; however, the acceleration time tended to be short in patients with mild or moderate tricuspid regurgitation.⁵ This may indicate that the Doppler acceleration index is not strongly affected by tricuspid regurgitation.

Although the acceleration time of pulmonary systolic flow is a useful index for the evaluation of pulmonary hypertension, it is affected by pulmonary arterial pressure, pulmonary blood flow, and histological changes in the pulmonary vascular bed. The acceleration time is a specific but not a sensitive index of pulmonary arterial pressure. An abnormal index indicates raised blood pressure with high peripheral resistance, but a normal index does not exclude raised blood pressure associated with high

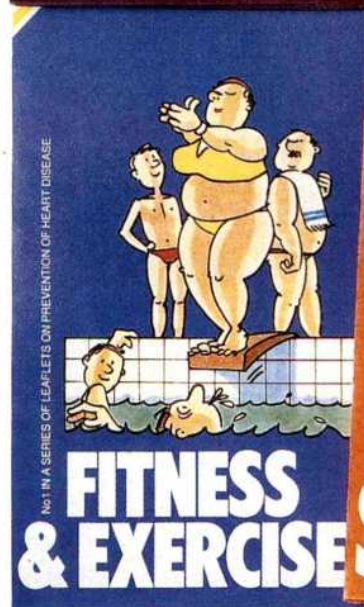
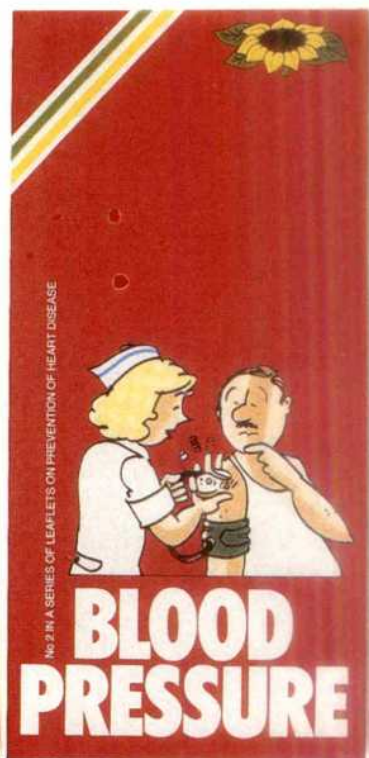
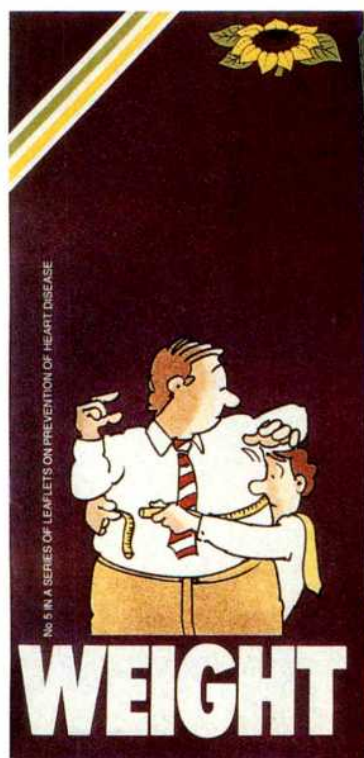
blood flow. Separate evaluation of each disease group should, however, improve the accuracy of this index. The correlation coefficient between acceleration time and mean pulmonary arterial pressure in patients with atrial septal defect was -0.87 (SEE 4.8 mm Hg), and that in the remainder of patients was -0.78 (SEE 8.0 mm Hg). This Doppler index is also suitable for the assessment of the pulmonary vascular bed.

We thank Miss Yoko Kojima for technical assistance.

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Relation between alcohol intake, myocardial enzyme activity, and myocardial function in dilated cardiomyopathy

Evidence for the concept of alcohol induced heart muscle disease

P J RICHARDSON, A D WODAK,* L ATKINSON, J B SAUNDERS,†
D E JEWITT

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SUMMARY Detailed drinking histories were taken in 38 patients in whom dilated cardiomyopathy was diagnosed by cardiac catheterisation and left ventricular biopsy. On the basis of the drinking history twenty patients were classified as being in an abstinent or light drinking group and eighteen patients as being in a heavy drinking group (daily alcohol intake in excess of 80 g or cumulative lifetime intake exceeding 250 kg). Activities of myocardial creatine kinase, lactate dehydrogenase, α hydroxybutyric dehydrogenase, malic dehydrogenase, and aspartate amino-transferase were all higher in the heavy drinkers and myocardial enzyme activity correlated with cumulative lifetime alcohol intake, maximum daily intake, and recent daily intake. Activities of creatine kinase, α hydroxybutyric dehydrogenase, and malic dehydrogenase correlated with ejection fraction, irrespective of the alcohol intake of the patient. These findings were not altered by exclusion of patients with hypertension.

The results indicate that among patients with dilated cardiomyopathy there is a group characterised by a high alcohol intake and raised myocardial tissue enzymes which supports the concept of alcoholic heart muscle disease as a distinct entity.

Although the association between excessive alcohol consumption and congestive (dilated) cardiomyopathy has long been known,^{1,2} a causal relation remains controversial.³ There are no studies that relate quantitative alcohol intake to myocardial damage, as there are for alcoholic liver disease.^{4,5} Indeed the clinical diagnosis of alcoholic heart muscle disease merely reflects the coexistence of global myocardial dysfunction in a heavy drinker in whom no other cause for myocardial disease has been found.

The development of endomyocardial biopsy has enabled histological assessment of the myocardium during life, but there are no specific histological features for alcoholic heart muscle disease.⁶ More recently, measurement of myocardial enzyme activity by microassay of biopsy specimens has been introduced.^{7,8} Wide differences in activities of several myocardial tissue enzymes were found among patients with dilated heart disease who were both haemodynamically and histologically indistinguishable.⁸ Preliminary data suggested that enzyme activities were highest in those patients diagnosed as having alcoholic heart muscle disease.⁹

The purpose of the present study was to assess the alcohol intake in a group of patients with dilated cardiomyopathy and to relate alcohol intake to myocardial enzyme activities and to myocardial function in order to establish objective evidence in support of the concept of alcohol induced heart muscle disease.

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Patients and methods

Seventy nine patients underwent myocardial biopsy over a period of 28 months; 41 had dilated cardiomyopathy. The other patients were diagnosed as having a specific heart muscle disease, including acute or healed myocarditis, ischaemic heart disease (with >50% stenosis of two or more vessels), or hypertrophic cardiomyopathy. Thirty eight of the 41 patients with dilated cardiomyopathy were investigated; the other three were not available for interview. No patient had any clinical evidence of abnormal nutrition and thiamine deficiency was excluded. We studied 36 men (aged 29–62 years (mean (SD) 49.5 (9.3)) and two women (aged 31 and 49 years). Twenty nine were white, three were Asian, and six were West Indian. Diastolic blood pressure was recorded at the fifth phase of the Korotkoff sounds.

ASSESSMENT OF ALCOHOL INTAKE

Patients were interviewed by one of two clinicians (ADW or JBS) who used a standardised interview schedule, which has previously been described and validated in a study of alcoholic cirrhosis,¹⁰ to ascertain lifetime alcohol consumption. The evolution of the patient's drinking habits was elicited by reference to key events such as school-leaving and changes in employment. With these as anchor points, questions were asked about the average weekly intake of alcohol, pattern of drinking, and the type of beverage taken during successive periods of a patient's life up to the time of presentation with heart disease. From this information various measures of alcohol intake were considered: (a) duration of drinking when daily alcohol intake exceeded 40 g and 80 g, (b) the corresponding mean daily intake during these periods, (c) the corresponding cumulative alcohol intake, (d) cumulative lifetime alcohol consumption, (e) maximum daily alcohol intake that was maintained for a period of at least a year, and (f) mean daily alcohol intake in the three months before investigation.

Six consecutive patients in the present study were interviewed on a subsequent occasion by the second observer independently to validate the technique in this group of patients. The intraclass correlation coefficients for the comparisons of cumulative lifetime consumption, duration of drinking >40 g alcohol/day, and corresponding cumulative intake for the two observers were 0.91, 0.89, and 0.80 respectively.

CARDIAC CATHETERISATION AND MYOCARDIAL BIOPSY

All patients underwent routine diagnostic catheter-

isation including selective coronary arteriography and left ventriculography. The left ventriculograms were obtained in the right anterior oblique projection at 30°. The systolic and diastolic frames were traced so that the left ventricular ejection fraction could be measured with a Summographic digitising table linked to a Commodore computer. The ejection fraction was calculated by application of Simpson's rule.¹¹ Coronary arteriography showed that in 30 patients all coronary vessels were free of important narrowing (patency >50%); in eight patients there was stenosis (>50%) of one vessel only, but in none was there occlusion of the vessel.

Endomyocardial biopsy samples of the left ventricle were obtained with the King's endomyocardial biptome and the Cordis long sheath introducer system. An average of four tissue samples were taken from each patient. At least two biopsy specimens were examined by routine light and electron microscopy as previously described.⁶ In 24 patients there was sufficient material for enzyme measurement and this was immediately frozen in liquid nitrogen and stored at -70°C.

MYOCARDIAL TISSUE ENZYME MICROASSAY

Biopsy samples of approximately 2–5 mg were weighed and homogenised in 0.25 mol/l ice cold sucrose. The following enzymes were assayed spectrophotometrically⁹ at 25°C under conditions of optimum pH and substrate concentration: creatine kinase, lactate dehydrogenase, α hydroxybutyric dehydrogenase, malic dehydrogenase, and aspartate aminotransferase. Protein was assayed by the method of Lowry *et al.*,¹² and enzyme activities are expressed as mU/mg of tissue protein; 1 mU corresponds to the hydrolysis of 1 μ mol of substrate/min.

OTHER LABORATORY INVESTIGATIONS

Routine haematological and biochemical tests, including liver function tests and serum γ glutamyltransferase measurements were performed on the day of admission.

DATA STORAGE AND STATISTICAL PROCEDURES

Data were stored and analysed in a CDC 6600 computer by means of the program suite *Statistical Package for the Social Sciences*.¹³ The distribution of variables was assessed by calculating the skewness (g3) and kurtosis (g4) and the Kolmogorov-Smirnov statistic Z; skewed data were transformed to log 10. Statistical significance was assessed by the χ^2 test (with Yates's correction where necessary) and Student's *t* test. Multiple regression analysis was performed with values for myocardial enzyme activity as the dependent variables; independent variables were

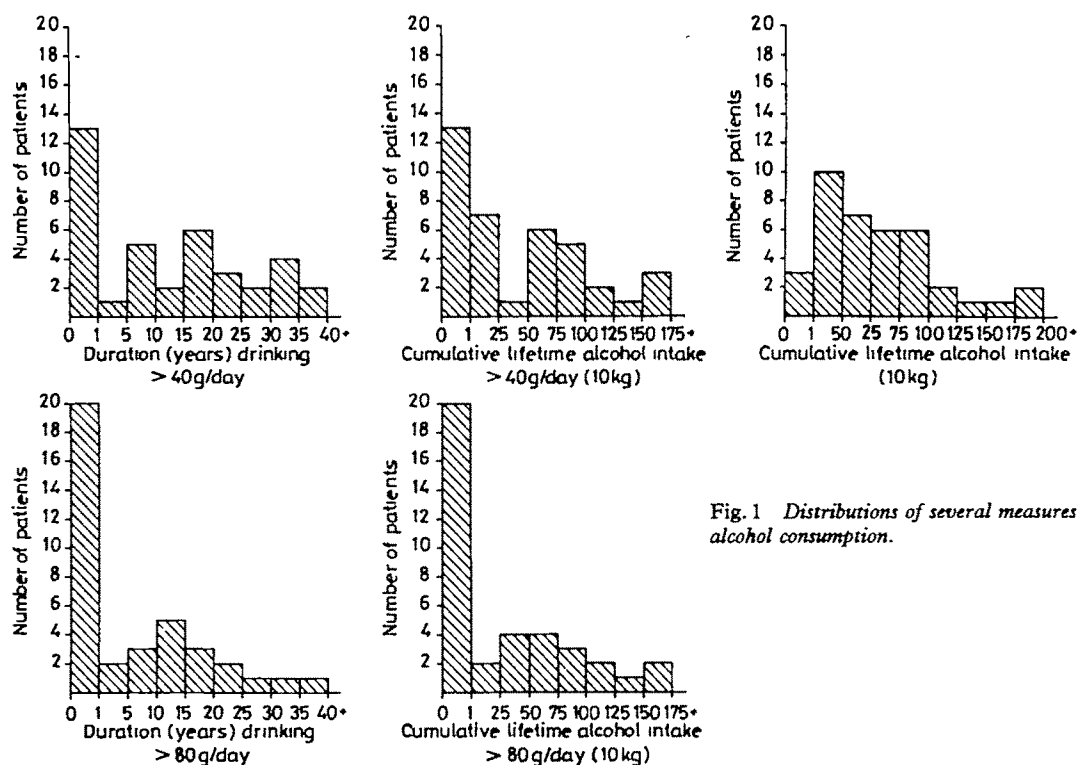


Fig. 1 Distributions of several measures of alcohol consumption.

entered in a stepwise fashion according to the F value for entry into the regression equation.

Results

DISTRIBUTION OF ALCOHOL CONSUMPTION

Figure 1 shows the distribution of several measures of alcohol consumption in the 38 patients. Three (8%) patients were teetotal. The distribution of cumulative lifetime intake was skewed ($g_3 = 1.9$) but it was unimodal. Thirteen (34%) patients had never drunk more than 40 g alcohol/day and in another seven (18%) patients the daily intake had never exceeded 80 g. When cumulative alcohol intake was calculated for periods when drinking exceeded these threshold amounts, a discontinuous distribution was apparent ($z = 0.94$ and 1.46 respectively).

While two of the three Asian patients had a cumulative lifetime intake <250 kg all six of the West Indian patients had a lifetime alcohol intake >250 kg.

RELATION OF MYOCARDIAL TISSUE ENZYME ACTIVITY TO ALCOHOL INTAKE

There were significant correlations between myo-

cardial enzyme activities and cumulative lifetime alcohol consumption, maximum daily intake, and recent daily intake (Table 1 and Fig. 2). Correlation analysis was not performed for the other measures of alcohol intake because of the discontinuities in their distributions. Tissue enzyme activities, except for aspartate aminotransferase, were significantly higher in the heavy drinking group compared with the abstaining or lightly drinking group (Table 2). There was no significant difference in ejection fraction between these two groups.

RELATION BETWEEN MYOCARDIAL ENZYME ACTIVITIES, MYOCARDIAL FUNCTION, AND BLOOD PRESSURE

The mean (SD) ejection fraction was 42.6 (16.2) and 12 (32%) patients had an ejection fraction of <30%, indicating severely impaired myocardial function. There was a correlation between certain myocardial enzyme activities and myocardial impairment as measured by the ejection fraction. The strongest relations were for creatine kinase ($r = 0.58$, $p < 0.01$), α hydroxybutyric dehydrogenase ($r = 0.52$, $p < 0.01$), and malic dehydrogenase ($r = 0.44$, $p < 0.05$).

Thirteen patients (34%) had a history of hypertension or were hypertensive (blood pressure >160/95 mm Hg) on admission. When these patients were excluded, the correlation between myocardial enzyme activities and alcohol intake remained significant. Although enzyme activities tended to be higher in hypertensive heavy drinkers than in normotensive heavy drinkers, the differences did not reach statistical significance.

RESULTS OF MULTIPLE REGRESSION ANALYSIS
A multiple regression analysis was performed (Table 3) to assess the relations between cumulative alcohol intake, myocardial function (ejection fraction), blood pressure, and myocardial tissue enzyme activities. This confirmed the relation between cumulative alcohol intake and myocardial enzyme activities and showed that ejection fraction was related to the activities of creatine kinase and α hydroxybutyric dehydrogenase independently of alcohol consumption. Neither systolic nor diastolic blood pressure had a significant independent association with tissue enzyme activities.

ALCOHOL INTAKE AND HAEMATOLOGICAL AND BIOCHEMICAL MARKERS OF ALCOHOL CONSUMPTION

There were weak correlations between cumulative lifetime alcohol intake, maximum daily intake, and recent alcohol intake and mean corpuscular volume ($r=0.32$, $p<0.05$, $r=0.29$, $p<0.05$, $r=0.32$, $p<0.05$ respectively). There was no significant correlation between alcohol intake and serum aspartate transaminase, alkaline phosphatase, or γ glutamyltransferase activities.

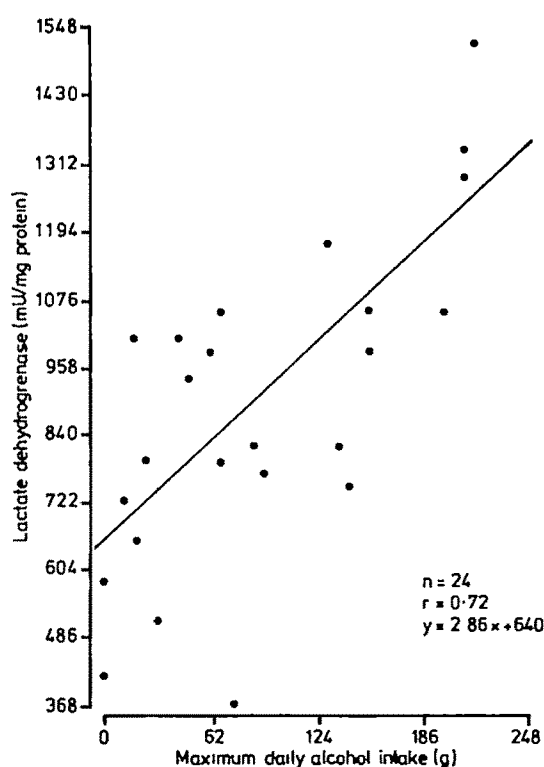


Fig. 2 Relation between myocardial tissue lactate dehydrogenase activity and maximum daily alcohol intake.

Table 1 Results of correlation analysis of myocardial enzyme activities with alcohol intake

	Cumulative lifetime alcohol intake		Maximum daily alcohol intake		Recent daily alcohol intake	
	r	p	r	p	r	p
Creatine kinase	0.56	<0.01	0.52	<0.01	0.35	<0.05
α hydroxybutyric dehydrogenase	0.59	<0.001	0.61	<0.001	0.49	<0.01
Lactate dehydrogenase	0.68	<0.001	0.72	<0.001	0.60	<0.001
Malic dehydrogenase	0.53	<0.01	0.56	<0.01	0.50	<0.01
Aspartate aminotransferase	0.19	NS	0.28	<0.10	0.26	NS

Table 2 Comparison of myocardial enzyme activities (mean (SE)) in abstinent or lightly drinking patients and in heavily drinking patients

	Abstinent or light drinkers (cumulative intake* <250 kg) (n=13)	Heavy drinkers (cumulative intake* >250 kg) (n=11)	p
Creatine kinase (mU/mg protein)	1674 (129)	2719 (226)	<0.001
α hydroxybutyric dehydrogenase	568 (39)	828 (57)	<0.001
Lactate dehydrogenase	730 (57)	1109 (69)	<0.001
Malic dehydrogenase	2089 (185)	2976 (185)	<0.005
Aspartate aminotransferase	510 (63)	661 (61)	<0.10

*When daily alcohol consumption exceeded 40 g/day.

Table 3 Results of multiple regression analysis of the relation between cumulative alcohol intake, ejection fraction, and blood pressure and myocardial enzyme activities

Enzyme		F	p	Multiple r
Creatine kinase	Cumulative alcohol intake (log 10)	4.59	<0.05	0.69
	Ejection fraction	9.54	<0.01	0.58
	Diastolic blood pressure	2.21	NS	0.73
α hydroxybutyric dehydrogenase	Cumulative alcohol intake (log 10)	8.09	<0.01	0.54
	Ejection fraction	5.86	<0.05	0.68
	Diastolic blood pressure	1.53	NS	0.71
Lactate dehydrogenase	Cumulative alcohol intake (log 10)	14.47	<0.02	0.65
	Ejection fraction	2.03	NS	0.69
	Diastolic blood pressure	2.03	NS	0.73
Malic dehydrogenase	Cumulative alcohol intake (log 10)	6.90	<0.02	0.51
	Ejection fraction	3.35	NS	0.61
	Diastolic blood pressure	2.04	NS	0.66
Aspartate aminotransferase	Cumulative alcohol intake (log 10)	6.42	<0.02	0.49
	Ejection fraction	1.89	NS	0.55
	Diastolic blood pressure	1.78	NS	0.61

Discussion

There is no clinical or histopathological difference between alcoholic heart muscle disease and dilated cardiomyopathy,^{6,14} and indeed there are some who do not accept the former as a distinct entity.¹⁵ In the present study patients with dilated heart muscle disease seemed to consist of two groups defined by their alcohol intake. The bimodal distribution of alcohol intake contrasts with the findings of surveys of alcohol consumption in the general population which show that alcohol intake has a unimodal distribution, with only 4% of males drinking more than 80 g/day.^{16,17} It is likely that the abstinent and lightly drinking patients represent the general population in terms of drinking ≤ 80 g alcohol/day; higher consumption is implicated in other forms of alcohol induced tissue damage such as cirrhosis of the liver.⁴ The possibility that some light drinkers are especially sensitive to the cardiotoxic effect of alcohol cannot, however, be excluded.

Unlike patients with alcoholic cirrhosis drawn from the same geographical area who drink more spirits (J B Saunders, A D Wodak, R Williams, unpublished observations) the heavy drinkers in our study were predominantly (83%) beer drinkers. The reason for this is unknown. Excess consumption of beer, because of its high carbohydrate content, may precipitate beriberi in patients with incipient thiamine deficiency, but none of our patients were thiamine deficient. Cobalt contaminated beer was implicated in the development of heart muscle disease in Canada several years ago, but this problem has now been eliminated.¹⁸ In previous studies alcoholic heart muscle disease was reported to be confined to men,^{1,2} and in the present study all the heavy drinkers were men. Again this contrasts with our experience of alcoholic liver disease, to which women are more susceptible.^{10,19} No hormonal or

other genetically determined factors predisposing to alcoholic heart muscle disease have been identified.²⁰ We found that as in alcoholic liver disease a pattern of continuous drinking rather than episodic drinking seems to be associated with alcoholic heart muscle disease. This may simply reflect the fact that a pattern of unremitting drinking is more likely to result in a higher cumulative alcohol intake than periodic drinking.

It has been suggested that dilated heart muscle disease may be caused by previous hypertension in subjects who have become normotensive after the development of impaired myocardial function (decapitated hypertension). The known association of alcohol use and hypertension may thus be a mechanism for the development of alcoholic heart muscle disease. The results of this study in which the correlations between myocardial enzyme activity and alcohol intake were unaffected by blood pressure do not support the notion of decapitated hypertension as the mechanism for development of alcoholic heart muscle disease.

The increases in myocardial enzyme activities in the heavy drinkers could be adaptive and may reflect chronic exposure to alcohol. Although alcohol can undergo esterification with fatty acid in the myocardium²¹ there is no evidence for appreciable myocardial metabolism of alcohol. In theory patients with alcoholic heart muscle disease may have always had abnormal tissue enzymes concerned with glycolysis and respiration and exposure to alcohol may have precipitated myocardial damage. This seems unlikely in the face of the close correlation between enzyme activity and exposure to alcohol.

Alternatively the enzyme changes may be secondary to myocardial tissue damage caused by an unrelated mechanism. Acute exposure to alcohol increases the concentration of several cardiac enzymes, including malic dehydrogenase, in the

coronary venous effluent²² and this may imply a direct cytotoxic action of ethanol. On this basis, however, it is difficult to explain how myocardial enzyme activities increase in response to chronic alcohol exposure.

The threshold dose of alcohol intake for heart muscle damage cannot be determined directly from studies such as the present one. The risk of developing cirrhosis at various levels of alcohol intake has been determined in epidemiological studies by comparison of the alcohol intake of patients with established cirrhosis with that of healthy age and sex matched patients drawn at random from the same geographical area. For alcoholic heart muscle disease, however, this would be a formidable undertaking in view of the comparative rarity of the condition and the fact that invasive investigation is necessary for a firm diagnosis of specific heart muscle diseases to be made.

Laboratory tests such as mean corpuscular volume, serum aspartate aminotransferase, and γ glutamyltransferase have been shown in several studies to be useful markers of excessive alcohol consumption. In the present study, however, although there was a correlation between mean corpuscular volume and alcohol intake it was not of practical use as a diagnostic marker and activities of serum enzymes were similar in the lightly drinking and heavily drinking groups. The best way to discriminate between these two groups seems to be a detailed lifetime drinking history. Serum activities of specific myocardial enzymes such as creatine kinase MB isoenzyme may prove to be a useful diagnostic tool, though so far this approach has proved to be disappointing.²³ Myocardial biopsy and measurement of tissue enzyme activity provide useful supportive evidence in favour of an alcoholic aetiology in patients with dilated heart muscle disease.

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Computed tomography: the investigation of choice for aortic dissection?

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SUMMARY Computed tomography has become established as complementary to aortography in the investigation of patients with suspected aortic dissection. Two cases of dissecting aneurysm are reported in which extensive aortography failed to show evidence of dissection. In both cases dissection was demonstrated by computed tomography. The diagnosis was confirmed in one case at operation and in the other case by follow up.

It is suggested that computed tomography is the diagnostic method of first choice in aortic dissection.

Effective management of acute dissection of the aorta is based on accurate and prompt diagnosis. Aortography has been the definitive method of diagnosis but computed tomography has recently become established as a complementary, and reliable, diagnostic method. The findings of computed tomography in acute dissection¹ parallel those of aortography. The diagnosis is confirmed by tomography if contrast material fills two or more channels in the aorta and if an intimal flap is identified, or (when there is no free flow of contrast material through the false channel) if intimal calcification is displaced inward from the aortic wall. Associated but non-diagnostic findings are thrombus in the aorta; mediastinal, pericardial, or pleural haematomas; and delayed filling and emptying of parts of the aortic lumen as shown by dynamic scanning after bolus injection of contrast material.

Computed tomography avoids the vascular catheterisation needed for aortography but is limited by low spatial resolution so that aortic branches cannot be assessed reliably. Artefacts can complicate the diagnosis of dissection by computed tomography,¹ and high quality tomograms may occasionally fail to demonstrate a dissection when one is present.² Nevertheless, several studies assessing computed tomography and aortography in the diagnosis of dissection have shown that the two investigations give comparable results.³⁻⁵ We describe two cases in

which computed tomography was better than aortography in the diagnosis of dissection.

Patients and methods

CASE 1

A 65 year old man presented with sudden, severe, sharp interscapular pain that had come on while he was driving. For 10 years he had had hypertension, which was treated with acebutolol and bendrofluazide. On admission he was still in pain and hypertensive (190/110 mm Hg), all the peripheral pulses were normal, there were no murmurs, and he was not in cardiac failure. The electrocardiogram was normal. A portable (antero-posterior) chest x ray suggested a wide superior mediastinum. A clinical diagnosis of acute aortic dissection was made.

At cardiac catheterisation the pressure in the ascending aorta was 160/100 mm Hg and the left ventricular pressure was 160/10 mm Hg. The aortic root and arch were examined by simultaneous biplane (right and left anterior oblique) cine-aortography at 50 frames/s on 35 mm film. Hexabrix 320 (60 ml) was injected at 30 ml/s for each aortogram and the output phosphors of Siemens 23 cm intensifiers were photographed with Arritechno cameras. A third single plane (posteroanterior), 25 frames/s, cine-aortogram of the descending thoracic and abdominal aorta was obtained by an otherwise similar technique. Routine cine films of left ventriculography and coronary arteriography completed the procedure and the angiograms were sub-

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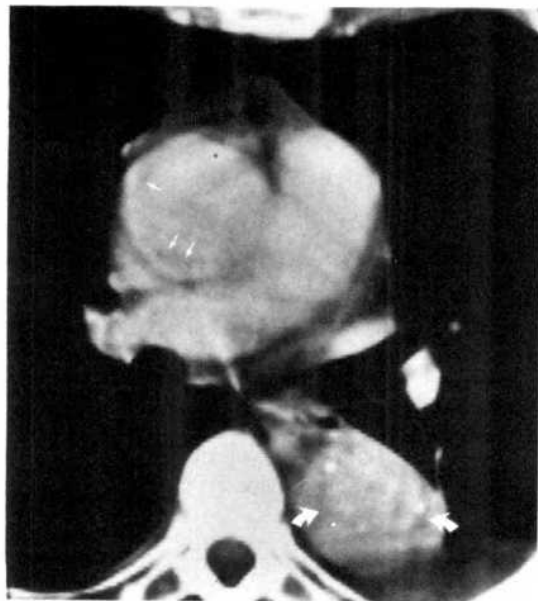


Fig 1 Computed tomography through mid-thorax of case 1 showing an intimal flap in ascending (straight arrows) and descending (curved arrows) aorta. Areas of calcification are seen within the lumen of the descending aorta. There are bilateral pleural effusions.

sequently displayed by a Cipro 35 projector. There was no aortic regurgitation and no sign of aortic dissection, though the thoracic aorta was slightly dilated throughout its course. The ventriculogram

was normal and the coronary arteries showed only trivial irregularities.

A posteroanterior chest radiograph taken three days later showed an enlarged heart, wide superior mediastinum, aortic dilatation, and small bilateral pleural effusions. Serum bilirubin concentration rose to $63 \mu\text{mol/l}$ (normal range $<17 \mu\text{mol/l}$). Thus despite the findings on aortography there was still a strong clinical suspicion of dissection. Eleven days after admission, computed tomography of the thorax and abdomen was performed by means of a Phillips Tomoscan 350 with a dynamic scanning program capable of obtaining 30 images within 5 min. Contrast enhancement was performed with 150 ml of Omnipaque 300 given by rapid peripheral venous injection. A dissecting aneurysm, extending from just above the aortic valve to the level of the aortic hiatus, was shown (fig 1). Pleural effusions were noted bilaterally.

Because the dissection shown by tomography affected the ascending and descending thoracic aorta, operation was considered to be necessary and he was transferred to another specialist centre for this. Aortography was repeated there (fig 2) and again showed no evidence of dissection; because of this and the patient's stable clinical condition, operation was not performed and the patient was discharged for outpatient follow up.

Six months later, computed tomography of the thorax was repeated. The pleural effusions had resolved. The diameter of the aorta in the lower thoracic region had increased to 7 cm, calcified thrombus was seen within the aorta (fig 3), and the crescent

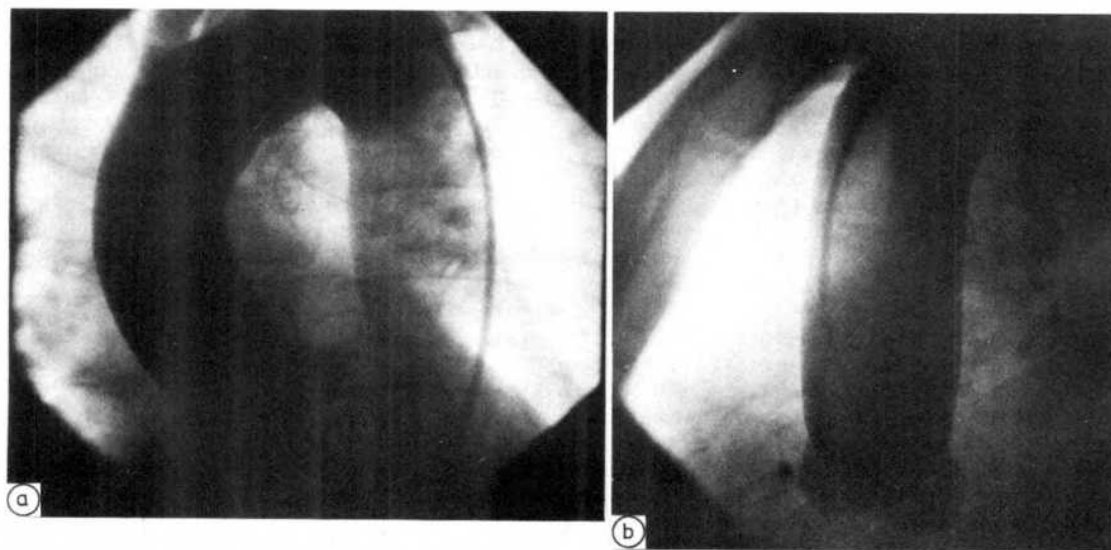


Fig 2 Aortograms in left anterior oblique (a) and lateral (b) projections in case 1. There are no features to indicate dissection.

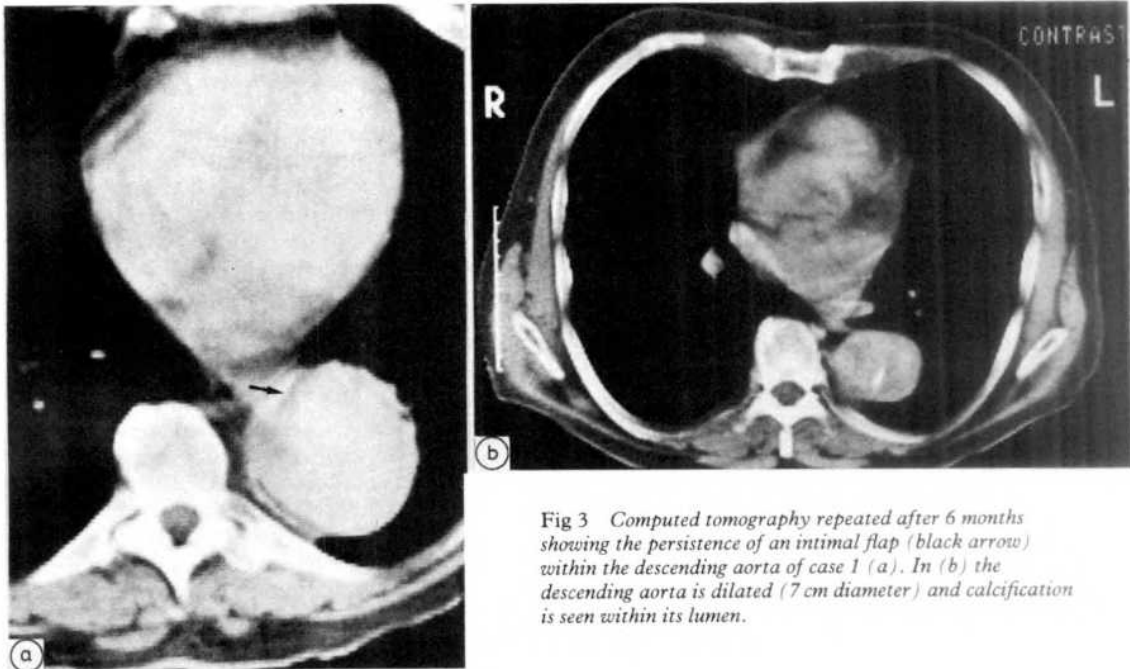


Fig 3 Computed tomography repeated after 6 months showing the persistence of an intimal flap (black arrow) within the descending aorta of case 1 (a). In (b) the descending aorta is dilated (7 cm diameter) and calcification is seen within its lumen.

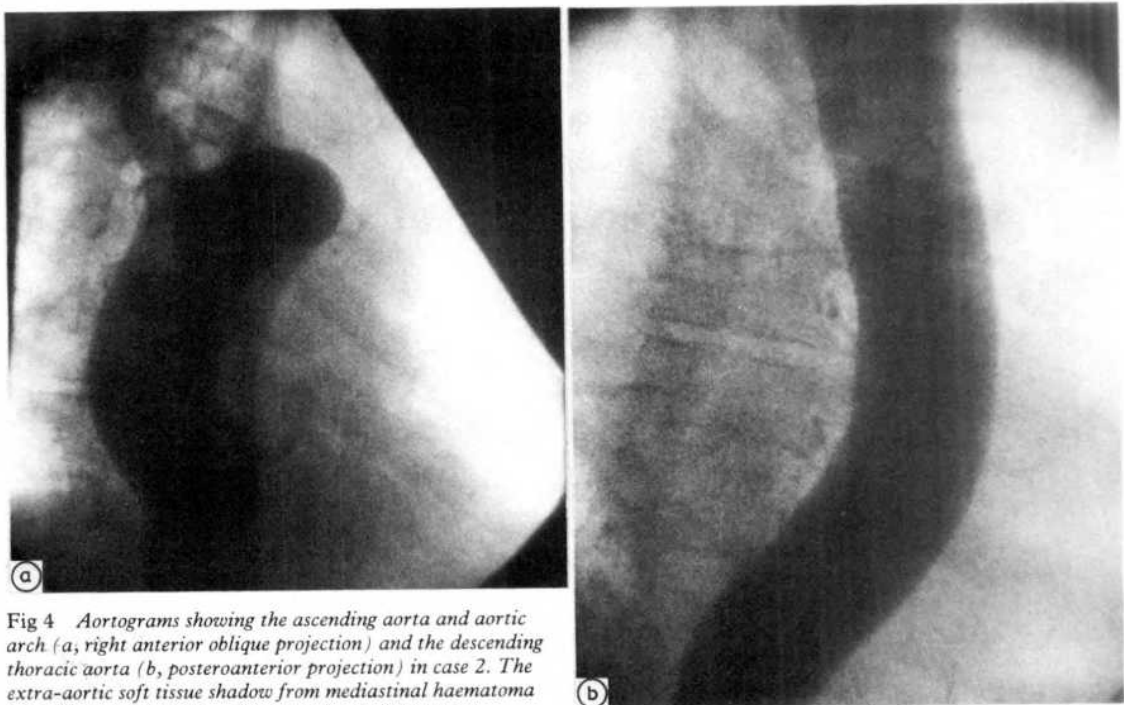


Fig 4 Aortograms showing the ascending aorta and aortic arch (a, right anterior oblique projection) and the descending thoracic aorta (b, posteroanterior projection) in case 2. The extra-aortic soft tissue shadow from mediastinal haematoma is visible (a). There is no direct evidence of dissection.

sign of dissection was apparent.

The patient remains well and has declined further investigation.

CASE 2

Sudden severe interscapular pain developed in a 72 year old man while he was gardening. The pain persisted and he was admitted to hospital the next day. Hypertension had been noted in the past but was not treated. His blood pressure was normal (120/80 mm Hg), all peripheral pulses were present, and there was no cardiac failure and no murmurs. The electrocardiogram was normal. The chest x ray showed a wide superior mediastinum and a small left pleural effusion. Aortic dissection (probably type III, DeBakey's classification⁶) was diagnosed. Computed tomography with contrast enhancement was performed to confirm the diagnosis and to assess the extent of the dissection. It was reported to show dissection involving both the ascending and descending aorta. Cardiac catheterisation and aortography were thus indicated as a preliminary to operation.

At catheterisation the aortic pressure was

130/80 mm Hg and left ventricular pressure was 130/5 mm Hg. Three aortograms were obtained by the techniques described in case 1. An extra-aortic soft tissue shadow that was responsible for the wide mediastinum was noted, but there was no evidence of dissection. In particular, the descending aorta was normal, with intact intercostal branches (fig 4). There was slight narrowing at the origin of the left subclavian artery. The findings on aortography deterred us from operation.

Over the next 36 hours the patient's clinical condition deteriorated. Blood pressure rose to 170/110 mm Hg and was controlled by nitroprusside infusion. He became dyspnoeic and wheezy. Serial chest x rays showed an increasing left pleural effusion. Review of the computed tomograms by another observer suggested that the diagnosis of dissection in the ascending aorta was mistaken though there was definite dissection of the descending aorta. Tomography was repeated and showed that the dissection of the aorta started at or just beyond the left subclavian artery, ending midway down the descending thoracic aorta. There was visible leakage

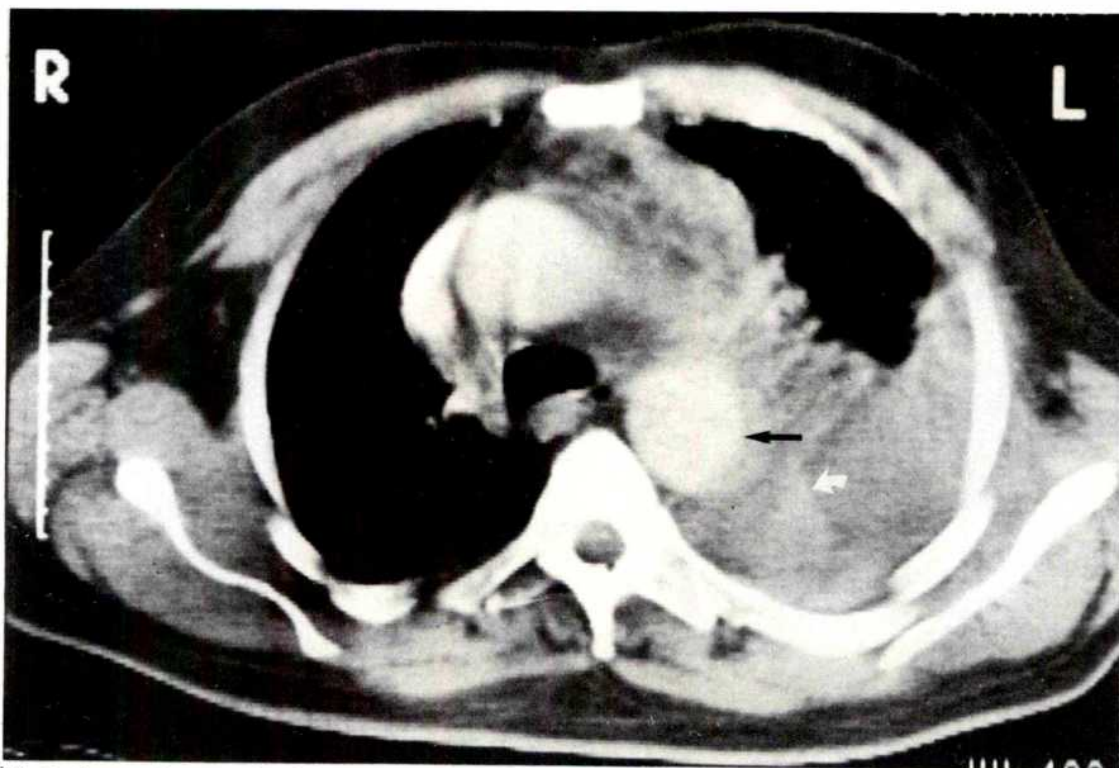


Fig 5 Computed tomography of thorax, after contrast enhancement, caudal to the aortic arch in case 2. The ascending aorta is normal. In the descending aorta contrast medium fills two channels separated by an intimal flap (black arrow). Within the large left pleural effusion there is an area of higher attenuation (curved arrow) showing contrast medium that has leaked from the aorta.

of contrast medium from the aorta into the left hemithorax (fig 5). An operation was performed immediately.

At operation a large amount of fresh and clotted blood was found in the left chest, and an extensive mediastinal haematoma was confirmed. The dissecting aneurysm was identified; it extended from just distal to the left subclavian artery to 7–8 cm into the descending aorta. There was no evidence of dissection in the ascending aorta. The aorta was cross clamped above and below the dissection and a 26 mm woven Dacron graft was sutured into place. Six months after operation the patient is leading an active life.

Discussion

In case 1 the clinical details were suggestive of aortic dissection. As was then our practice, the initial investigation was by cardiac catheterisation and aortography. Although the study was of good quality, no evidence of dissection was found. Continuing clinical suspicion of dissection led us to perform computed tomography, and as a result the patient was referred to another institution for operation. There, normal findings on repeat aortography were interpreted as excluding the diagnosis of dissection and operation was not undertaken. Therefore we do not have surgical confirmation of the diagnosis of dissection, but the diagnosis is irrefutable on the follow up tomographic study (fig 3).

In case 2 the clinical details were suggestive of a type III dissection (DeBakey's classification). Computed tomography confirmed the diagnosis of dissection but was reported as showing dissection also in the ascending aorta (therefore type I). Because type I dissection is managed by operation, cardiac catheterisation was undertaken before surgery. Good quality aortograms, however, showed no evidence of dissection. Computed tomography was repeated because of deterioration in the patient's clinical condition; it showed a type III dissection leaking into the left hemithorax. On preoperative review, the first tomographic report of involvement of the ascending aorta was considered to have been mistaken. The findings at operation confirmed the findings of the second computed tomography.

In a shocked and deteriorating patient with severe aortic regurgitation or tamponade or both caused by proximal aortic dissection, cross sectional, echocardiography at the bedside may be all that is possi-

ble before the patient is taken to theatre. Our experience with computed tomography leads us to regard it as the preferred initial diagnostic method in the more stable patient. If tomography shows that the dissection is confined to the descending aorta and there are no complications such as mediastinal compression and continuing haemorrhage into the thorax (as in case 2), medical management is appropriate and aortography may be avoided. If, however, dissection affects the ascending aorta, cardiac catheterisation to assess the severity of aortic regurgitation and to obtain high resolution images of the coronary arteries and aortic arch branches is generally regarded as a prerequisite of operation. Aortography is better than computed tomography in localising the intimal tear, but this may not be essential to operative management.⁷

Aortography is generally regarded as the definitive investigation for acute dissection of the aorta but false negative results have been reported.⁸ Computed tomography is a reliable alternative diagnostic method, and the two cases reported here suggest that it is in fact superior to aortography.

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Influence of profuse sweating on systolic time intervals

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SUMMARY The influence of profuse sweating on systolic time intervals was investigated. Systolic time intervals were recorded in 21 healthy men before and after sauna bathing. After sauna bathing the ejection time was significantly shortened and the pre-ejection time and ratio of pre-ejection time to ejection time (PEP:ET) were significantly increased. The upper limit of the PEP:ET ratio is generally believed to be 0.42 and this ratio increases when left ventricular performance is impaired. Before sauna bathing the PEP:ET ratio was <0.42 in all 21 men, but after sauna bathing it was >0.43 in six (28.5%) of them. Systolic time intervals measured after profuse sweating can give a false impression of cardiac function.

Systolic time intervals obtained from simultaneous recordings of electrocardiograms, carotid pulse tracings, and phonocardiograms have been widely used to assess left ventricular function in various clinical settings.¹⁻⁶ The relation of these intervals to heart rate, cardiac output, and stroke volume⁷ and their alterations during heart failure¹ and in response to autonomic drugs⁸ have been examined in detail. We noticed that systolic time intervals were sometimes abnormal in healthy subjects who had been sweating profusely, and this prompted us to investigate the effect of sweating on systolic time intervals in a group of healthy men.

Patients and methods

We studied 21 healthy men (age range 22-40 years; mean 26.5 years) who used a Finnish sauna with an air temperature of 80-90°C and relative humidity of 30-40%. The amount of fluid lost was estimated from the decrease in body weight and ranged from 1.5 kg to 3.0 kg (mean 2.2 kg). We measured blood pressure, heart rate, haematocrit, and serum electrolyte concentrations, and we recorded systolic time intervals in all the men before they entered the sauna and an hour after bathing.

Carotid pulse tracings, phonocardiograms, and

electrocardiograms were recorded simultaneously on a Fukuda model 100 A, six channel oscillographic recorder at a paper speed of 100 mm/s. We used the electrocardiographic lead that most clearly demonstrated the onset of ventricular depolarisation (usually lead II or a precordial lead). A contact microphone (Fukuda MA 250) was placed over the upper part of the precordium in the best position for recording the initial high frequency vibration of the first and second heart sounds. The carotid arterial pulse was recorded from a pick up with a time constant of 2.0 s (Fukuda TY 303).

The following phases of the cardiac cycle were measured directly: (a) the total electromechanical systolic interval (Q-II) estimated from the onset of the QRS complex to the first frequency vibrations of the aortic component of the second heart sound (II); (b) the left ventricular ejection time (ET) measured from the beginning upstroke to the trough of the incisura of the carotid pulse tracing; (c) the interval between the first heart sound and the second heart sounds (I-II) measured from the onset of the first heart sound to the second heart sound; (d) the pre-ejection period (PEP) calculated by subtracting ET from Q-II; (e) PEP:ET obtained by dividing PEP by ET; and (f) Q-SI derived by subtracting I-II from Q-II. Results for Q-II, ET, and PEP were corrected ((Q-II)c, ETc, and PEPc) for heart rate by means of Weissler's equation.¹

The systolic time intervals were calculated as means from 10 consecutive complexes. To avoid interobserver variations⁹ systolic time intervals were all measured by one experienced physician.

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Table Systolic time intervals in 21 healthy men before and after sauna bathing

Case no	Age	Ht (%)		(Q-II)c (ms)		I-II (ms)		ETc (ms)		PEPc (ms)		Q-I (ms)		PEP:ET		HR (bpm)		BW (kg)	
		B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A	B	A
1	30	42.4	45.5	541.3	550.5	370	350	410.1	418.5	131.2	122.0	60	85	0.34	0.31	53	55	76.5	73.5
2	28	44.0	42.4	515.5	534.7	340	340	420.5	381.9	117.0	152.8	60	75	0.32	0.46	55	57	62.0	60.0
3	23	41.9	43.0	542.0	553.5	340	310	424.0	399.5	118.0	154.0	55	65	0.30	0.47	70	85	64.2	62.5
4	23	42.5	43.8	549.2	553.1	375	360	413.4	403.7	135.8	149.4	65	65	0.35	0.42	52	61	56.5	55.0
5	24	40.0	42.0	523.9	531.8	335	355	395.3	398.6	128.6	133.2	65	55	0.36	0.37	59	58	55.0	52.5
6	24	45.5	48.5	530.2	528.1	350	330	420.4	398.7	109.8	129.4	50	70	0.27	0.36	62	61	68.0	65.0
7	25	42.0	45.0	549.7	550.2	375	350	416.9	415.4	132.8	134.8	55	70	0.34	0.35	57	62	63.0	61.1
8	30	44.0	44.5	558.3	542.8	340	320	409.1	400.6	149.2	142.2	65	80	0.42	0.40	73	68	55.1	53.4
9	32	48.0	51.5	549.2	548.6	375	340	413.4	407.2	135.8	141.4	65	70	0.35	0.39	52	66	54.7	52.0
10	40	42.0	44.5	521.2	547.0	310	320	412.4	399.0	108.8	148.8	60	80	0.28	0.43	72	70	75.0	72.6
11	30	43.8	46.3	534.3	535.3	305	280	416.1	398.1	118.2	137.2	55	60	0.31	0.47	83	93	66.5	64.0
12	22	46.3	49.0	522.9	514.5	350	350	428.3	401.5	94.6	113.0	70	70	0.22	0.29	49	45	80.0	77.0
13	23	43.9	45.1	526.6	526.3	360	360	408.2	400.1	118.6	126.2	70	55	0.30	0.34	46	53	66.5	64.5
14	24	46.3	47.7	516.5	523.9	320	340	415.5	410.3	101.0	113.6	60	60	0.25	0.29	65	59	59.0	57.5
15	23	49.6	50.5	544.4	542.3	355	350	408.8	427.1	135.6	115.2	55	60	0.37	0.28	64	63	77.0	74.5
16	27	43.2	46.0	560.1	540.2	340	350	442.1	405.4	117.4	134.8	50	60	0.28	0.37	81	62	52.5	49.0
17	29	52.9	53.3	560.2	628.5	360	325	440.4	419.5	119.8	159.0	70	75	0.28	0.45	62	85	92.5	90.0
18	28	45.5	46.8	518.6	543.0	330	325	392.2	396.0	126.4	147.0	50	50	0.36	0.44	66	80	47.0	45.5
19	22	42.3	45.2	547.0	508.6	330	315	419.0	392.2	128.0	116.4	70	55	0.33	0.32	70	66	67.7	66.2
20	25	52.5	55.9	511.8	513.3	345	300	403.6	399.1	108.2	144.2	45	60	0.28	0.42	58	73	71.0	68.5
21	25	45.3	47.9	543.9	533.9	355	350	410.3	400.3	133.6	133.6	65	60	0.35	0.37	59	59	61.0	58.0
Mean	26.5	44.9	46.9	536.5	540.5	345.7	334.3	415.2	403.5	117.2	130.9	60.0	65.7	0.31	0.38	62.3	65.8	65.2	63.0
SD	4.3	3.4	3.6	15.6	24.1	20.1	21.2	12.1	10.1	13.3	14.1	7.6	9.5	0.047	0.059	10.0	11.8	10.7	10.6
value			$p < 0.001$		NS		$p < 0.01$		$p < 0.01$		$p < 0.001$		$p < 0.05$		$p < 0.001$		NS		$p < 0.001$

Ht, haematocrit; (Q-II)c, corrected total electromechanical systolic interval; I-II, interval between the first and second heart sounds; ETc, corrected left ventricular ejection time; PEPc, corrected pre-ejection period; Q-I, interval between onset of ventricular depolarisation and the first heart sound; HR, heart rate; BW, body weight; bpm, beats per minute; SD, standard deviation; NS, not significant; B, before sauna bathing; A, after sauna bathing.

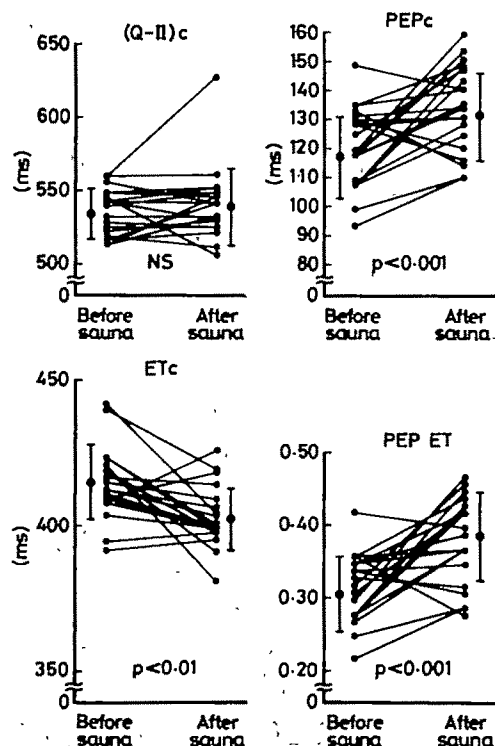


Fig. 1 After sauna bathing (Q-II)c was not significantly altered, PEPc was significantly increased, and ETc was significantly shortened. PEP:ET was significantly increased after sauna bathing.

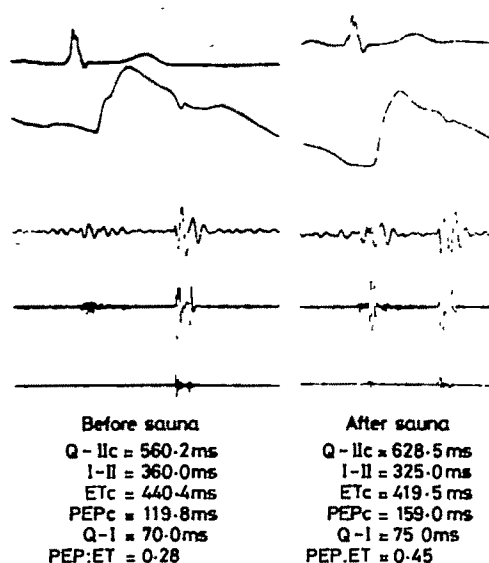


Fig. 2 (Q-II)c, PEPc, and PEP:ET were increased and ETc was decreased after sauna bathing.

Results

The Table summarises all the data obtained before and after sauna bathing. This Table and Fig. 1 show significant increases in PEPc, Q-I, and PEP:ET; a significant decrease in ETc; and no change in (Q-II)c after sauna bathing. Before sauna bathing

PEP:ET was <0.42 in all the men, whereas after sauna bathing it had increased to >0.43 in six (28.5%) men.

The mean haematocrit increased slightly from 45.9% before sauna bathing to 46.9% after sauna bathing. Heart rate, blood pressure, and serum electrolytes (such as potassium, calcium, and magnesium) were not significantly changed after sauna bathing. Fig. 2 shows data for a representative case in which (Q-II)c, PEPc, and PEP:ET increased and ETc decreased after sauna bathing.

Discussion

Systolic time intervals can be measured at the bedside and they give useful information on cardiac function. They are cheap, carry no risks, and give immediate results, and so they can be performed repeatedly. Because systolic time intervals may be considerably influenced by extracardiac factors, they can give a misleading assessment of cardiovascular function. Beat to beat variations¹⁰ and observer variations⁹ may lead to their misinterpretation. We have occasionally seen abnormal systolic time intervals in apparently healthy subjects who have been sweating profusely. These findings prompted us to examine the effect of sweating on systolic time intervals. Sweating induced by sauna bathing is considered to resemble physiological sweating more closely than does sweating induced by exercise or drugs.

In an attempt to exclude the direct influences of sauna bathing and to ensure stable cardiac status, we recorded systolic time intervals an hour after sauna bathing. Heart rate and blood pressure were unchanged after sauna bathing, but there were significant increases in PEPc, (Q-I) time, and PEP:ET, and a significant decrease in (I-II) time and ETc. There was no essential change in total electromechanical systole (Q-II)c.

ETc, PEPc, and PEP:ET are more commonly used in daily clinical practice than the other variables that are derived from systolic time intervals. Generally speaking, ETc is shortened by a decrease in stroke volume,¹ by an increase in left ventricular ejection velocity (as seen in hyperthyroidism¹¹ or anaemia¹²), and by inotropic agents such as digitalis¹³ or isoproterenol.¹⁴ The ETc shortening observed in this study was probably due to a decrease in stroke volume. PEPc is prolonged by a decrease in stroke volume or myocardial contractility¹ and by negative inotropic agents such as beta blockers.¹⁴ A decrease in stroke volume was considered to be responsible for the prolongation of PEPc observed in the present study.

In the present study the PEP:ET ratio increased because PEP was increased and ET was shortened. This ratio is widely used to assess ventricular function. The upper limit of normal is believed to be

0.42, and the ratio is increased when function is impaired. We found that after sauna bathing the ratio increased to >0.43 in six (28.5%) of 21 men. This result indicates that systolic time intervals measured after profuse sweating can give a false impression of cardiac function. This should be borne in mind when systolic time intervals are measured at high temperature and high humidity, in febrile patients, and in subjects who have been exercising vigorously.

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Case reports

Unusual echocardiographic appearance of intracardiac thrombi in a patient with endomyocardial fibrosis

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SUMMARY A five year old girl presented with a four-month history of recurrent heart failure, which subsequently proved to be caused by endomyocardial fibrosis. There was no evidence of valvar disease. Echocardiography showed several echogenic masses with echolucent centres within the cardiac cavity. Histological examination showed that these masses were partly organised thrombus.

Endomyocardial fibrosis is rarely found in a patient who has never been to the tropics. The classic clinical course is that of a short lived pyrexial illness followed by a period of weeks or months of progressive deterioration of cardiac function leading to the development of heart failure. It is typically complicated by valvar dysfunction (usually mitral regurgitation) and occasionally by intracavity thrombus formation.¹ In our patient there was no evidence of valvar dysfunction but there was progressive heart failure.

Case report

A five year old Greek girl presented with an acute exacerbation of a four month illness. This had begun with a two day episode of fever and dyspnoea that led to her being admitted to a local hospital where left ventricular failure was diagnosed and treated with digoxin and diuretics. Initially she had recovered well, but she was readmitted on several occasions with exacerbations of heart failure, with digoxin toxicity, or with chest infections.

She presented to this hospital because her illness had become worse over the preceding two weeks. She had become weak, sleepless, and had begun to vomit. She was anorexic and had some abdominal pain. Her parents noted that she had begun to look

rather pale and yellow.

On examination she was obviously ill, slightly jaundiced, but afebrile. Her blood pressure was 120/80 mmHg and she had a tachycardia of 120 beats/min. The jugular venous pressure was raised and her liver, which was enlarged 7 cm below the costal margin, was smooth and soft. The spleen was not palpable. A third heart sound was heard but there were no signs of valvar heart disease.

The electrocardiogram showed a sinus tachycardia of 140 beats/min with some left axis deviation (-90°). Voltage criteria indicated a left atrial abnormality and left ventricular hypertrophy. The chest x ray showed signs of left heart failure with upper lobe diversion of blood and pulmonary plethora, and there was appreciable cardiomegaly (cardiothoracic ratio 12.5:19 cm). Whole body x ray computerised tomographic scanning and ultrasound studies of the liver showed no evidence of a tumour.

A cross sectional echocardiogram was performed through the precordial, apical, and subcostal windows in standard projections. Both ventricles were dilated and globally hypokinetic. All valves appeared to be normal. At least five masses were seen within the left ventricle and one or more of them appeared to move freely about the ventricular cavities in a manner quite unlike that of a mural thrombus. Several appeared to be attached to the ventricular wall by a thin pedicle. There were at least two similar masses in the right ventricle, both of which did not appear to move within the cavity. The masses were spherical with echogenic perimeters; however, their

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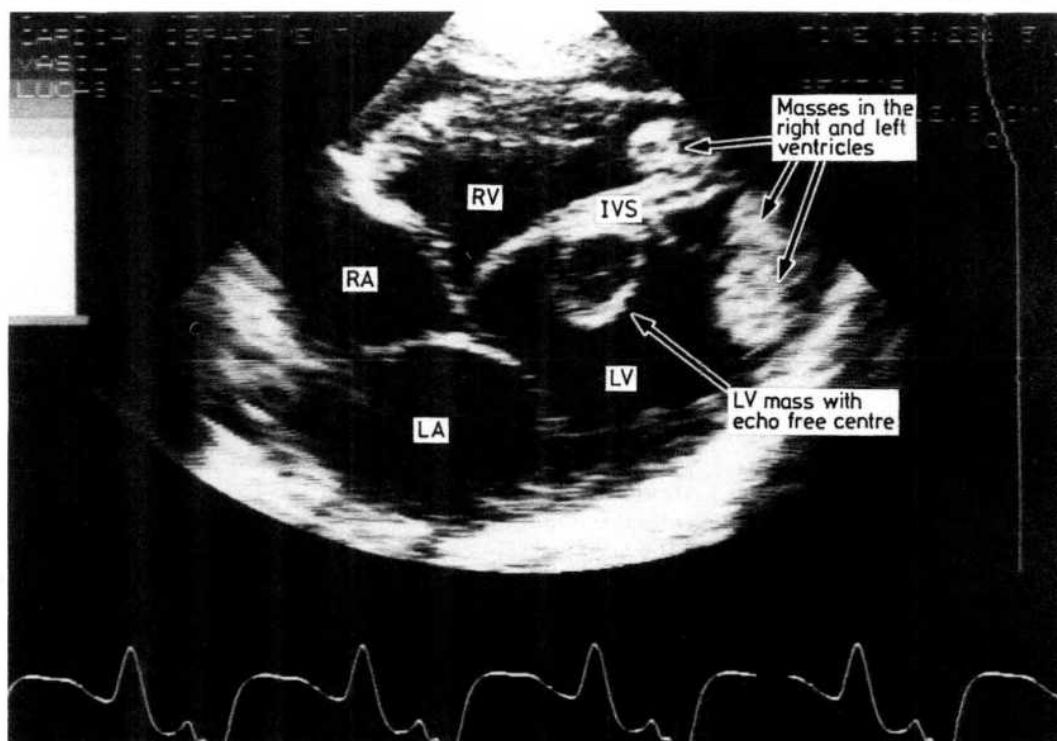


Figure A frame from the cross sectional echocardiogram via the subcostal window. This shows three of the masses with relatively echo-free centres lying within the cavity of the left ventricle and one mass at the apex of the right ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle; IVS, interventricular septum.

centres were echo free. When the masses were viewed in real time the perimeters were seen to "wobble" in a way that suggested that these structures were easily deformed. The figure shows a frame recorded from the subcostal window.

In view of the haemodynamic risk of such a tumour mass in the ventricles and because of the need to establish a tissue diagnosis, the patient had left ventriculotomy with biopsy of both the myocardium and the intracardiac material. At operation the surgeon found that the interior of the left ventricle contained a large amount of recent blood clot, which was aspirated. There was frond-like material in the clot that was thought to be organised clot or possibly tumour tissue. The wall of the ventricle was found to be roughened and yellowish after aspiration of this material.

On the day after operation the patient deteriorated and died. Histological examination of the intracardiac material showed that it was an organising thrombus; there was no evidence of tumour. Vascular granulation tissue had filled up the intertrabecular spaces and the underlying myocardium showed some interstitial scarring but was otherwise

unremarkable. Acute phase endomyocardial fibrosis was diagnosed at necropsy.

Discussion

In this patient the diagnosis of endomyocardial fibrosis was not suspected on clinical grounds. Although the clinical course was compatible with endomyocardial fibrosis, the fact that the patient had never been to the tropics made the diagnosis very unlikely. Echocardiography was undertaken as a part of the routine investigation of unexplained heart failure, and the finding of intracavity masses was unexpected. In view of the progressive ill health of the patient, the working diagnosis was that of tumour, either primary or secondary. Physical examination and whole body x ray computed tomography showed no other site of tumour, and, therefore, operation was undertaken both for diagnostic and therapeutic reasons.

Echocardiography is the best method for imaging intracardiac structures and for the detection of intracardiac masses. Cross sectional echocardiographs showing masses with relatively echo-free centres

have been described in patients with cystic tumours, but only a few of these have been caused by intracavity masses²⁻⁴—these were cases of atrial myxomas with cysts or areas of haemorrhage within them. There are no reports of appearances quite like those seen in our patient. Initially this echocardiograph was interpreted as showing multiple tumours with liquid, possibly necrotic, centres.

Review of the echocardiograph in the light of the findings at operation and necropsy indicated that the appearances were due to recently formed thrombus moving freely in the ventricle; the centre of the thrombus was not yet organised and was echo-free. We believe that the wobbly appearance of the perimeter was caused by a thin shell of organised thrombus surrounding a liquid centre.

We thank Professor M J Davies, British Heart Foundation Cardiovascular Pathology Unit, St George's

Hospital Medical School, London, for performing the histological examination.

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Intracoronary thrombolytic treatment: another hazard

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SUMMARY A patient with acute anterior myocardial infarction was treated with intracoronary thrombolysis. At cardiac catheterisation the first contrast injection into the left coronary artery dislodged some of the thrombus occluding the left anterior descending coronary artery. The thrombus embolised into the circumflex artery where fortunately it fragmented without causing occlusion.

The risk of detachment of thrombus should be borne in mind when angiography and thrombolytic treatment are considered in acute myocardial infarction.

Myocardial infarction is nearly always associated with thrombotic occlusion of the coronary artery supplying the area of infarcting myocardium.¹ Intracoronary thrombolytic treatment can restore vessel patency if treatment is begun early after the onset of infarction.² Evidence that thrombolytic treatment might reduce mortality^{3,4} is only just emerging, however, and limitation of infarct size may be confined to those patients in whom thrombolysis is achieved soon after the onset of infarction.^{5,6} The risks and benefits of thrombolysis are still being debated.

Coronary angiography in the context of acute myocardial infarction carries a definite but unknown risk. Five of a series of 83 patients undergoing angiography before thrombolysis died⁷; in two patients death was attributable to the angiographic procedure. Our case report illustrates a hitherto unrecognised and potentially hazardous complication of angiography in acute myocardial infarction.

Case report

A 56 year old man was admitted two hours after the onset of typical cardiac pain. The admission electrocardiogram showed the features of an acute anterior myocardial infarction (ST segment elevation in leads VI-V5, I, and aVL; ST segment depression in

leads II, III, and aVF). He was considered to be suitable for thrombolytic treatment with streptokinase for which he gave written consent.

Left coronary arteriography was performed by the Judkins technique from the right femoral artery by means of an 8F 4 cm left coronary catheter. This was primed with contrast medium (Hexabrix 320) when it reached the descending thoracic aorta and it was advanced easily under fluoroscopic control into the left coronary ostium. Simultaneous biplane (posteroanterior and lateral; then right and left anterior oblique) 35 mm cine films of hand injections of 8 ml Hexabrix 320 were recorded at 50 frames per s with Arritechno cameras from Siemens 15 cm image intensifiers. The angiograms were subsequently displayed and analysed frame by frame with a Cipro 35 projector.

A dominant left coronary artery was shown with proximal occlusion of the left anterior descending branch and stenoses (more than 75% reduction in luminal diameter) in the circumflex artery and its obtuse marginal and posterior descending branches.

The cine film of the first injection of contrast medium clearly showed the occlusion site in the left anterior descending artery (at point "a" in Fig. a) by the seventh frame from the beginning of contrast injection. Seven frames later, contrast medium suddenly filled the left anterior descending artery more distally (to point "b" on Fig. b), and there was a coincidental appearance of an intraluminal filling defect ("c" in Fig. b). During the course of the next 14 frames the filling defect, which remained constant in shape and size, moved first retrogradely to

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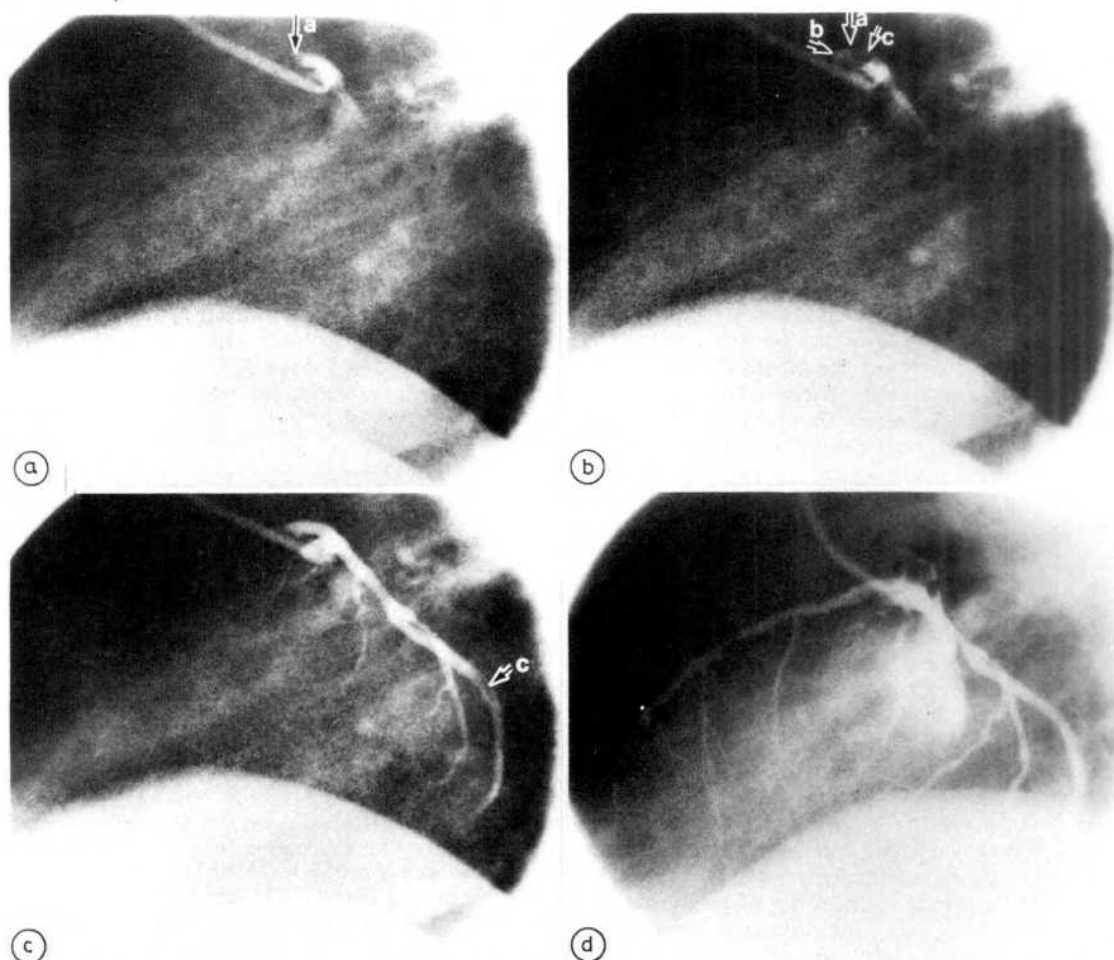


Figure Left coronary arteriogram in the left lateral view. Frames a, b, and c are from the same run of cine film, taken at 50 frames/s after the first injection of contrast into the left coronary artery. In frame a, "a" marks the site of occlusion in the left anterior descending artery. At this time, seven frames from the beginning of contrast injection, the circumflex artery is only just beginning to be opacified. In (b), taken seven frames later, "c" marks the filling defect caused by the thrombus which has been displaced from the occlusion in the left anterior descending artery. Contrast now fills the left anterior descending artery more distally to "b" (for comparison "a" on frame (a) is reproduced on frame (b)). In (c), taken 14 frames after (b), the circumflex artery is well opacified but the left anterior descending artery remains occluded. The thrombus (shown by "c") has embolised from the left anterior descending artery into the circumflex artery. (d) is a frame from a cine film taken after successful thrombolysis and angioplasty of the left anterior descending artery. There is no obstruction of circumflex branches.

the bifurcation of the left coronary artery and then anterogradely into the circumflex artery ("c" in Fig. c). Over the next eight frames it fragmented as it passed into distal circumflex branches. This sequence is interpreted as representing detachment and embolisation of part of an occluding thrombus in the left anterior descending artery during the course of the single injection of contrast medium. The catheter tip, clearly seen in the two planes, was in the ostium of the left coronary artery, well clear of

the origin of the left anterior descending artery. Careful analysis of the cine film showed no evidence of embolus from the catheter itself.

No symptoms or electrocardiographic changes accompanied the dislodgement of thrombus. The branches of the circumflex artery were all patent on subsequent arteriograms (Fig. d).

Streptokinase infusion into the left coronary artery (4000 IU per min) achieved thrombolysis in 30 min. Repeat angiography showed an important

stenosis at the site of the previous occlusion. Balloon angioplasty of the stenosis of the left anterior descending artery was easily performed; the angiographic result was good (Fig. d) and the patient returned to the coronary care unit. His progress was uneventful until four days later when he had electrocardiographic evidence of reinfarction and ventricular tachycardia and then ventricular fibrillation developed from which he could not be resuscitated.

Necropsy showed an extensive recent transmural myocardial infarction affecting the anterolateral wall and two thirds of the interventricular septum. An old inferior myocardial infarction was also noted. There was thrombosis of the proximal 2 cm of the left anterior descending artery. The right and circumflex coronary arteries showed severe atheromatous disease without evidence of recent thrombotic occlusion.

Discussion

The complication rate of routine coronary angiography has been well documented. Deaths are almost invariably related to severe, often left main stem, coronary disease.⁸ Coronary embolism is rare (0.07%).⁸ In acute myocardial infarction and intracoronary thrombolysis it may be difficult to separate the morbidity and mortality of the procedure from that of the underlying infarction. In the report by Serruys *et al* two deaths were attributable to the procedure; the tip of the coronary catheter dislocated the thrombus from the left anterior descending artery towards the circumflex artery.⁷ These workers drew attention to the peculiar anatomy in these two patients (very short left main stem artery with proximal thrombosis of the left anterior descending artery).

In our patient the left main stem artery was a good length and the occlusion of the left anterior descending artery was about 2 cm from its origin. Embolisation of the occluding thrombus occurred as a result of the injection of contrast medium, not as a result of any contact of the catheter with the thrombus. We believe this to be the first report of such an occurrence. Once the thrombus had become detached its subsequent course was determined by the flow of blood and continued contrast medium injection.

There were no untoward immediate sequelae in this patient, presumably because the thrombus fragmented as it passed distally in the circumflex branches. The consequences of an acute occlusion of the circumflex artery in a patient with an acute occlusion of the left anterior descending artery and a left dominant system could have been disastrous.

Embolisation of coronary thrombus may well occur more readily in acute myocardial infarction when the thrombus is fresh and probably loosely attached to the coronary artery. We have demonstrated that contrast injection alone can cause detachment of thrombus. This potential hazard should be considered when the risks and benefits of intracoronary thrombolytic treatment are being assessed.

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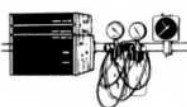
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Successful balloon aortic valvotomy in a child with a pulmonary hypertensive duct and aortic valve stenosis

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SUMMARY A ten year old boy with pulmonary hypertension and a ductus arteriosus had severe aortic valve stenosis relieved by balloon aortic valvotomy. Subsequent aortic regurgitation was mild. This procedure avoided open heart operation, which would have been hazardous in this patient.

Percutaneous transluminal balloon valvotomy for pulmonary valve stenosis has become an established procedure¹ and its use in many patients has avoided open heart surgery. There are more problems and greater risks when the technique is used to relieve aortic valve stenosis.²

We report the effectiveness of balloon aortic valvotomy in a child in whom the risk of open heart surgery was considerable.

Case report

This ten year old boy was first noted to have a murmur in the neonatal period. When he was three years old investigation showed a ductus arteriosus and pressure in the systemic circulation was equivalent to that in the pulmonary artery. His condition was considered to be inoperable. Reinvestigation when he was eight confirmed the presence of the ductus arteriosus. Mean pulmonary artery pressure was 63 mm Hg, the systemic mean pressure was 60 mm Hg and did not fall (65 mm Hg) when 100% oxygen was given. The pulmonary vascular resistance (total) was calculated from an assumed oxygen consumption to be 21.7 units.

He was referred to the National Heart Hospital to be considered for heart and lung transplantation. Examination suggested that there was also a complicating left sided lesion because there were small car-

otid pulses and an intense systolic ejection murmur at the left sternal edge. For this reason reinvestigation was performed and specific attention was paid to the left outflow tract. This showed severe valvar aortic stenosis with a peak aortic gradient of 101 mm Hg (mean gradient 60 mm Hg and valve area 0.3 cm²) and a domed, thickened and mobile valve on angiography (fig a). The left ventricular filling pressure was normal (12 mm Hg) and the pulmonary arteriolar resistance was 22.1 units with a ratio of 0.7 between the pulmonary artery resistance and the systemic resistance (cardiac output was measured by thermodilution). Oxygen saturation of blood in the ascending aorta was 85% and in a femoral artery it was 75%.

Symptoms of hypoxia developed earlier than expected in this boy, and we wondered whether the aortic valve disease had accelerated the development of pulmonary vascular disease. There was, therefore, a case for relieving the obstruction even though the pulmonary vascular resistance was unlikely to fall. The obvious difficulties of cardiopulmonary bypass with temporary closure of the duct and the hazard of severe pulmonary vascular disease in the post-operative period made open valvotomy a formidable undertaking.

On 5 March 1985, percutaneous balloon valvotomy was performed under general anaesthesia. Before valvotomy the aortic gradient was 92 mm Hg (66 mm Hg mean). A Gensini catheter and 260 cm guide wire were introduced percutaneously into the femoral artery and advanced to the left ventricular apex. A 1.8 cm balloon was advanced over the wire until two thirds of the balloon was below the aortic

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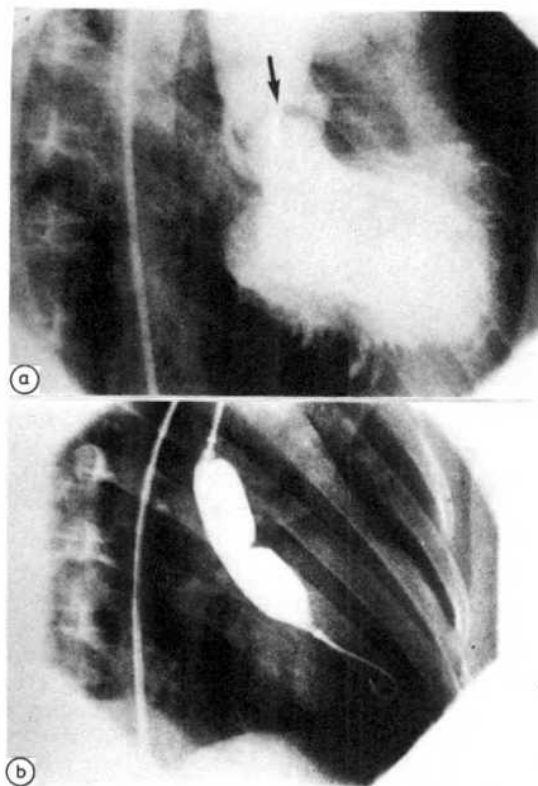


Figure (a) Left ventricular angiography before aortic valvotomy, showing domed aortic valve stenosis. Catheter almost fills the orifice (arrow). (b) Almost fully inflated balloon passed across the left ventricular outflow tract indented by stenosed aortic valve just before the constriction was relieved.

valve plane. The balloon was rapidly inflated twice with dilute contrast to a maximum pressure of 3.5 bar (350 kPa). "Waisting" of the balloon (fig b) and its subsequent disappearance were noted on the first occasion. Subsequent gradient measurement across the aortic valve indicated successful relief of the stenosis (peak and mean gradients 10 mmHg) and aortography showed mild aortic regurgitation with an aortic pressure of 130/80 mm Hg.

Recovery from the procedure was uneventful, and the systolic thrill disappeared clinically; the murmur

was short with a late click and soft immediate diastolic component. The signs of pulmonary hypertension remained. At an outpatient follow up five months later, the boy's mother reported that he was less breathless and not cyanosed. Aortic regurgitation had not increased, echocardiography indicated a considerable reduction of the left ventricular hypertrophy, and Doppler studies suggested only a "trace" of aortic regurgitation.

Discussion

The prognosis of patients with pulmonary hypertension and ductus arteriosus without other lesions is relatively good because symptoms appear late, usually in adolescence, and cases may survive until the fifth or even sixth decades provided cerebral abscess and rupture or thrombosis of pulmonary arteries do not occur. This boy with severe aortic valve stenosis became disabled earlier and he was unlikely to survive beyond 20 years. We were able to relieve the aortic valve stenosis by balloon valvotomy; this avoided exposing him to the considerable risk of open heart operation.

Balloon valvotomy can cause severe or catastrophic aortic regurgitation and may fail in patients with dysplastic valves. Open aortic valvotomy is safer and more likely to achieve a better haemodynamic result. In special circumstances, however, in which the risks of surgery are unusually high, as in this patient with irreversible pulmonary hypertension, we recommend balloon valvotomy. We hope that there will be improvement in this boy's condition that will delay the need for heart and lung transplantation. We still prefer open aortic valvotomy for usual cases of aortic valve stenosis.

We thank Dr James E Lock for his useful advice.

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Left atrial rupture in osteogenesis imperfecta

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SUMMARY A 60 year old man with features of osteogenesis imperfecta presented in biventricular failure with evidence of mitral regurgitation. He responded to conventional treatment but later collapsed and died at home. Necropsy showed a haemopericardium caused by a tear in the left atrium. There was also rupture of the mitral chordae tendineae.

Osteogenesis imperfecta is a heterogeneous group of disorders of collagen biosynthesis¹ characterised by osseous fragility and a familial incidence. Recent biochemical advances and genetic studies have allowed a detailed classification to be established.²

One subtype (Sillence type I) is characterised by blue sclerae, deafness, and fractures with or without dentinogenesis imperfecta. As with other connective tissue disorders (such as Marfan's syndrome and Ehlers-Danlos syndrome), cardiovascular anomalies have been described³ but they are rarely fatal.

Case report

A 60 year old white man was admitted after a second episode of paroxysmal nocturnal dyspnoea associated with a recent history of breathlessness. He could walk only ten yards, and had a productive cough but no orthopnoea.

He first presented with dyspnoea of sudden onset four years earlier when a pansystolic murmur was found. Atrial fibrillation subsequently developed. This responded to symptomatic treatment and he was discharged from follow up. He had smoked cigarettes, 10 per day, for many years and had a history of multiple fractures. There was no family history of cardiovascular disease; his father and one paternal cousin also had multiple fractures. His three children were well; a fourth died in infancy. There are no details of this child's illness.

Examination showed a small, kyphotic man who was anxious but in no distress. He was deaf, with

blue sclerae, normal tympanic membranes, and a short right leg. He was in fast atrial fibrillation with evidence of left ventricular enlargement, mitral regurgitation, and biventricular failure. An electrocardiogram showed atrial fibrillation and left ventricular hypertrophy. Chest x ray confirmed cardiomegaly, kyphosis, and upper lobe blood diversion. Routine blood testing showed polycythaemia, increased concentrations of hepatic enzymes, and arterial hypoxaemia. M mode echocardiography showed concentric left ventricular hypertrophy with early systolic prolapse of the posterior mitral valve leaflet and late systolic ballooning of the same leaflet (fig 1). The left atrium was normal. Spirometry showed a forced expiratory volume (1 s) of 1580 ml and a forced vital capacity of 2090 ml (ratio 76%).

He was treated with digoxin, diuretics, and verapamil and he responded well. He discharged himself on the tenth day. The next day, his general practitioner assessed him as being in good health, but later that same day he collapsed and died. Necropsy showed a well nourished man with a barrel chest. The ribs were fragile and could be cut easily with simple scissors. Death was caused by a haemopericardium which was the result of left atrial rupture. The heart was considerably enlarged (625 g) with predominant left ventricular hypertrophy but the myocardium was healthy. The mitral valve ring was enlarged (16 cm, normal, range 5.3-10.2 cm), the valve cusps showed ballooning and prolapse that is typical of the floppy valve syndrome, and four elongated posterior chordae tendineae were ruptured. The left atrium was dilated and there were many endocardial striae (fig 2); some were haemorrhagic. The atrial wall adjacent to the left atrial appendage was ruptured at the site of a similar endocardial split. The position was appropriate for a jet

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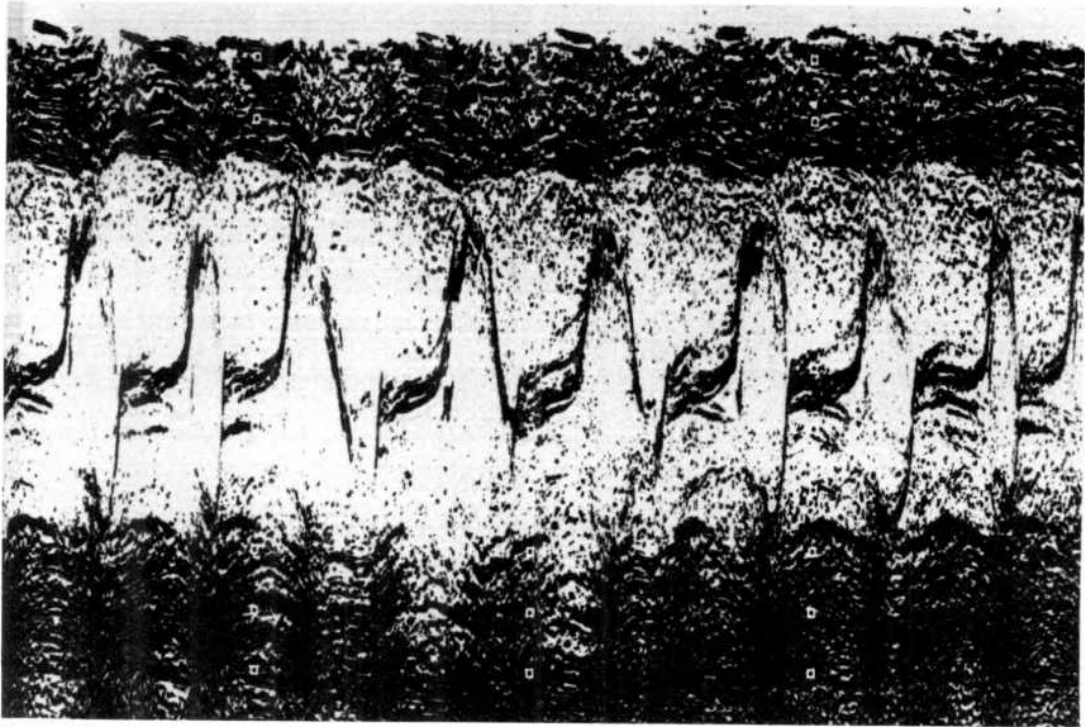


Fig 1 *M mode echocardiograph showing early systolic prolapse of the posterior mitral valve leaflet.*

lesion from the regurgitant mitral valve. There was a haemorrhage in the atrial wall that was continuous with the pericardial haematoma.

Apart from a congested "nutmeg" liver all other organs were normal. Histological examination confirmed myxoid and myxomatous degeneration of

the mitral valve fibrosa. Intact chordae tendineae showed areas of wasting; those that were ruptured showed thin ruptured ends with excess elastic tissue on the frictional surfaces. The atrial wall showed linear splits in the subendocardial zone with interstitial haemorrhage or early organisation and scarring.



Fig 2 *Inspection of the left atrium showed areas of linear splitting in the endocardium and adjacent striae.*

Discussion

Mitral regurgitation with myxoid degeneration of the valve cusps is recognised in Marfan and Ehlers-Danlos syndromes.³ The heart, however, is rarely affected by osteogenesis imperfecta.⁴ In some cases recognition of aortic valve disease has been followed by valve replacement.⁵ In a review of 23 reported cases of osteogenesis imperfecta, with serious cardiovascular disease, White *et al* found that 48% had abnormal mitral valves causing mitral regurgitation, whereas 87% had aortic regurgitation. The same group studied 20 symptom free patients and found cardiovascular abnormalities in all of them (seven were hypertensive and 13 has a soft late systolic murmur).⁶ Only one had echocardiographic mitral valve prolapse and none had important mitral regurgitation. Valve disease in osteogenesis imperfecta may be amenable to operation; however, the peri-operative risks are increased both by a generalised bleeding tendency of uncertain cause and by decreased mobility.⁷

It is difficult to determine the frequency of valve disease in osteogenesis imperfecta because it is such a heterogeneous disorder. Four major types have been described,² each with a distinct familial pattern. Each type may be expressed with variable penetrance, but in a given family the clinical features are similar. Only patients with the milder types of the disease (I and IV) generally survive to adulthood, hence reported cases must belong to these groups although specific features are not reported.

The floppy mitral valve is increasingly recognised in normal individuals⁸ and in patients with collagen disorders. Ninety cases were found in 1984 routine necropsies⁹; this resembled the frequency that was found by echocardiography.¹⁰ Few of the cases in which the chordae tendineae were intact had a valvar abnormality related to the cause of death; the floppy valve contributed to death in 39% of cases in which

there was rupture of the chordae tendineae. The floppy valve is also found as an isolated abnormality in cases of sudden death; in most there are important ruptured chordae and mitral regurgitation. Haemopericardium is not reported.

Thus our patient appears to have had a mild form of osteogenesis imperfecta type I, with blue sclerae, deafness (predominantly conductive), and fragile bones. His death from left atrial rupture was an unusual complication of this generalised connective tissue disorder.

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Myocardial infarction in a young man with systemic lupus erythematosus, deep vein thrombosis, and antibodies to phospholipid

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SUMMARY From the age of 17 a young man had recurrent venous thrombosis, with pulmonary embolism on two occasions. Laboratory investigations showed increased DNA binding, thrombocytopenia, positive antinuclear antibodies, and immunoglobulin A deficiency. A plasminogen activator deficiency was suspected because the euglobulin lysis time was considerably prolonged. Variant lupus was diagnosed. He had a severe myocardial infarct at the age of 20 and subsequent investigations showed the presence in serum of the lupus anticoagulant and antibodies to cardiolipin. The presence of these antiphospholipid antibodies explains the features of his illness and establishes that this case fits into a subset of systemic lupus erythematosus characterised by thrombotic events.

Venous occlusion, particularly deep leg vein thrombosis and thromboses of the renal vein and inferior vena cava,¹ are all reported to be more common in a type of systemic lupus erythematosus in which there are circulating antibodies to phospholipid (the lupus anticoagulant)² and cardiolipin.³ Arterial occlusions, resulting from an arteritis/vasculitis or thrombotic disease of large vessels such as the aorta and its major branches,⁴ the subclavian and brachial arteries,⁵ and other larger vessels occur infrequently in systemic lupus erythematosus. An association between occlusions of the large arteries and antiphospholipid antibodies occasionally leads to gangrene and bowel infarctions.^{6,7}

We describe a patient with a plasminogen activator deficiency who had a myocardial infarction at the age of 20 years. Later antibodies to phospholipid were found in his serum.

Case report

In March 1978 a boy aged 17 complained of right

sided pleuritic chest pain which was diagnosed as Bornholm disease. In June 1978 he complained of pain in the left calf which resolved after 10 days; a deep venous thrombosis was diagnosed. In September 1978 venous thrombosis occurred in the left leg; a radioisotopic scan showed evidence of pulmonary embolism and a venogram showed a left iliofemoral blockage. In February 1979 subcostal and shoulder pain developed and right upper lobe pneumonia was diagnosed. Investigations at the Royal Melbourne Hospital showed that he had a positive test for antinuclear antibody (titre 1:1000 with a speckled pattern) and a positive test for antibody to DNA (there was binding of 43% in a Farr-type assay; normal <20%). The serum concentration of immunoglobulin G was increased to 16.9 g/l (normal <16 g/l) and immunoglobulin A was considerably reduced (<0.15 g/l). Concentrations of the serum complement components C3 and C4 were within normal limits, and the Venereal Disease Research Laboratories test was negative. The lupus erythematosus cell test was negative.

A plasminogen activator deficiency was diagnosed because the euglobulin lysis time was prolonged. A blood pressure cuff (80 mm Hg) was applied for 10 minutes to induce release of tissue plasminogen acti-

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Figure Coronary arteriogram showing slight narrowing of the left anterior descending coronary artery just beyond the first diagonal branch. The distal third of the left anterior descending coronary artery is diffusely narrowed and there is poor filling of its terminal branches.

vator from the vein wall. The results were: pre-stress, 6 hours (normal 2–4 hours) and post-stress, 5 hours 23 minutes (normal 40–80 minutes). He was treated with ethyloestrenol.

In May 1979 he suffered another pulmonary embolus and venography again showed a clot in the left femoral vein. Swelling of the left thigh and calf persisted. The spleen was palpable. His illness was diagnosed as variant lupus. He was treated with warfarin and the ethyloestrenol was continued. The antinuclear antibody test remained positive (titre 1:100–1:500, speckled pattern) as did the test for DNA antibody.

Further tests for euglobulin lysis time were performed from 1979 to 1980 inclusive. The results pre-stress ranged from 5 h 40 min to 6 h 16 min and post-stress from 4 h 40 min to 5 h 44 min. Ethyloestrenol was stopped as it was deemed to be ineffective. In July 1981 he complained of persistent chest pains after a weekend visit to a ski resort. Myocardial infarction was diagnosed on the basis of electrocardiographic findings, raised serum activities of cardiac enzymes (creatinine kinase was successively 508, 392, and 97 IU/l), a raised leucocyte count (12.1

$\times 10^9/l$), and evidence of left ventricular infarction from a technetium-99m (pyrophosphate) scan. A chest x ray showed a moderately enlarged heart. A coronary arteriogram (fig) showed normal right, left main, and circumflex arteries, and slight narrowing of the left anterior descending artery and a hypokinetic left ventricular wall. Laboratory tests at this time showed a raised erythrocyte sedimentation rate (73–93 mm/hour), kaolin partial thromboplastin time within normal limits, a normal platelet count, and a negative Coombs' test. The euglobulin lysis time was not measured during this admission.

In February 1983 the patient was seen at Hammersmith Hospital. He was symptom free and physical examination was normal. The left thigh and calf were swollen and there was bluish discolouration of the left foot. The platelet count was decreased ($88 \times 10^9/l$) and the prothrombin time was 23 s (normal 14 s). The kaolin partial thromboplastin time was 95 s (control 40 s) and the clotting abnormality was not corrected by the addition of normal plasma, indicating the presence of an inhibitor of coagulation. The Oxford disseminated lupus erythematosus inhibitor test confirmed that the inhibitor present was of the lupus type. A strongly positive anticardiolipin antibody test provided further support for this finding.

The antinuclear antibody test was weakly positive (titre 1:40, speckled pattern), but the test for DNA antibody was negative (12%) and antibodies to extractable nuclear antigens were not demonstrable. Immune complexes were shown to be present in serum by the monoclonal rheumatoid factor binding assay.

The concentration of serum immunoglobulin G was again raised (17.7 g/l) and, as previously, the concentration of immunoglobulin A was considerably reduced (<0.45 g/l). The euglobulin lysis time was within normal limits.

In October 1984 the patient was well, apart from a swollen left thigh and calf and venous stasis in the left foot. He is now receiving continuous anticoagulation with warfarin and has had no further problems.

Discussion

This patient initially presented with an illness characterised by recurrent venous thromboses and pulmonary emboli. Originally, on the basis of a greatly prolonged euglobulin lysis time, plasminogen activator deficiency was diagnosed. The fluorescent antinuclear antibody test was positive, but because all the criteria for a diagnosis of systemic lupus erythematosus were not met variant lupus was diagnosed. He was treated with ethyloestrenol which at

the time was believed to ameliorate states of decreased fibrinolytic activity,⁸ but this seemed ineffective, and later he received warfarin. Despite anticoagulant treatment he had a myocardial infarct 3 years later when he was 20. Serum tests for the lupus anticoagulant (antiphospholipid antibodies) and antibody to cardiolipin were later found to be positive. His disease belongs to a subgroup of systemic lupus erythematosus in which thrombotic events are associated with the presence of antiphospholipid antibodies. These are immunoglobulins of the G or M class, and they inhibit the activity of the prothrombin activator complex (factor V, factor Xa, calcium, and phospholipid). They appear to react specifically with phospholipids including those of platelets. The presence of these antibodies is paradoxically associated with venous, and occasionally arterial, thrombosis and several theories have been formulated to account for this effect.

Carreras *et al* demonstrated that an immunoglobulin G fraction from a patient with high lupus anticoagulant activity reduced prostacyclin production in rat aortic ring and human myometrium.⁹ Sanfeliippo and Drayna reported decreased kaolin induced fibrinolytic activity in their patients with the lupus anticoagulant,¹⁰ and decreased fibrinolytic activity was also found in four similar patients described by Elias and Eldor.¹¹ Prekallikrein (Fletcher factor) may be inhibited by the lupus anticoagulant and the possible consequent impairment of fibrin clearance may result in clotting. The prolonged euglobulin lysis time in our patient was evidence of impaired fibrinolytic activity in the plasma.

Kaolin induced fibrinolytic activity does not necessarily correspond to the activity measured by the conventional euglobulin lysis time, which was performed initially in a clinical setting to define a coagulation defect in our patient. More detailed assays to elucidate further the cause of prolonged euglobulin lysis time were not performed because they were not routinely available at that time.

Coronary occlusion with myocardial infarction is infrequent early in the course of systemic lupus erythematosus, but may supervene late in the disease, usually as a result of severe atherosclerosis or coronary arteritis.¹² Landi *et al* first mentioned the occurrence of myocardial infarction in a patient with the lupus anticoagulant.¹³ In addition, the presence of anticardiolipin antibodies and lupus anticoagulant has been linked with recurrent fetal loss, cerebral infarction, pulmonary hypertension, and chorea.¹⁴ These antibodies are likely to have been involved in the genesis of the coronary occlusion in the present patient. Although the kaolin partial thromboplastin time was normal at the time of his admission for the investigation of the deep vein

thrombosis in 1979, one normal result does not exclude their presence. The aetiology of the low immunoglobulin A concentration can only be speculative. In the absence of the usual causes, such as coeliac disease or nephrotic syndrome, the most likely explanation is the autoimmune disease itself. Low immunoglobulin A concentrations are occasionally associated with systemic lupus erythematosus.

In conclusion, in the absence of other diagnostic criteria for systemic lupus erythematosus this patient was described as having variant lupus because of a raised DNA antibody assay result and the presence of antinuclear antibody. He demonstrated the features recently described as occurring in a specific subset of patients with systemic lupus erythematosus in the presence of the lupus anticoagulant and antibodies to cardiolipin, namely recurrent venous thromboses and pulmonary embolism, major arterial thrombosis, and thrombocytopenia.

The anticardiolipin antibodies can now be measured by means of a solid phase assay system; this can be performed on patient sera and is cheap, sensitive, and reproducible.¹⁴ The lupus anticoagulant test has the disadvantage of variations in methodology from laboratory to laboratory and the need for freshly prepared plasma for reliable results. A recent study from Sweden has shown a high frequency of anticardiolipin antibodies in young survivors of myocardial infarction and a strong correlation with post-infarct thrombotic events, including reinfarction.¹⁵

We suggest that anticardiolipin antibodies should be sought in all younger patients with unexplained thrombotic disease including arterial thrombosis.

We thank Dr G R V Hughes and Dr A E Gharavi for their assistance in this case.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 25 to 27 November 1986, and the closing date for receipt of abstracts was 11 July 1986.

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts will be 6 January 1987.

Thrombosis and haemostasis

The XIth Congress of the International Society on Thrombosis and Haemostasis will be held in Brussels on 6 to 10 July 1987. Inquiries to: H R Lijnen, PhD, Centre for Thrombosis and Vascular Research, Campus Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

Pierre Rijlant prize

Applications are invited for the Pierre Rijlant prize for cardiac electrophysiology. For further details write to Professor A Verniory, Secretary, Pierre Rijlant Foundation, Rue Ducale 1, B-1000 Brussels, Belgium.

Correspondence

α receptors and ventricular tachycardia after clonidine withdrawal

Sir,

We have reported on a patient in whom repetitive ventricular tachycardia was induced by clonidine withdrawal.¹ In this patient up regulation of myocardial α adrenoreceptors was implicated in the genesis of tachycardia because intravenous phenolamine completely suppressed the tachycardia. It has been suggested that stimulation of α receptors enhances the induction of triggered automaticity,^{2,3} which is said to be a cause of repetitive ventricular tachycardia.⁴ We have some additional comments to make on the mechanism inducing this tachycardia.

In our earlier case report we could not determine whether the α_1 or α_2 receptors were mainly responsible for the tachycardia.¹ α_1 receptors, which are present in the heart, are more likely to have been responsible for tachycardia in our patient. But in contrast to the dramatic effectiveness of phenolamine in our patient the effect of orally administered prazosin, a selective α_1 blocker, on tachycardia was limited despite its considerable hypotensive effect. The plasma concentration of prazosin may have been too low to suppress the development of tachycardia.

Alternatively, α_2 receptors may have been involved in the tachycardia. α_2 receptors have not yet been found in the human heart, but their presence in the sheep heart has been suggested by Mugeli *et al*, who showed that α_2 receptors participated in noradrenaline induced triggered automaticity.³ Clonidine reduces sympathetic outflow from the brain, and such a reduction can produce up regulation of postsynaptic α_2 receptors.⁵ Clonidine is a partial α_2 agonist but α_2 receptors are reported to be relatively resistant to desensitisation,⁵ although the withdrawal of an extraordinary large dose of clonidine can induce down regulation of vascular α_2 receptors.⁶ The behaviour of human cardiac postsynaptic α receptors after withdrawal of long term clonidine is not known. But the possibility that α_2 receptors participate in the genesis of the tachycardia that follows clonidine withdrawal cannot be ruled out. In our patient the short term effect of clonidine was not known, because the dose (0.225 mg per day), was too low to produce an acute reduction in blood pressure.

Thus both α_1 and α_2 receptors may be involved in the genesis of the ventricular tachycardia that follows clonidine withdrawal. Evaluation of the effectiveness of selective α_1 and α_2 and, if possible, β blocker and calcium antagonists on the arrhythmias may give more information on this condition.

In clonidine withdrawal syndrome it may be advisable to prescribe a full dose of clonidine or non-selective α blocker and gradually taper the dose.

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Abrupt withdrawal of atenolol in patients with severe angina: comparison with the effects of treatment

Sir,

The correspondence (1986;55:112-3) arising out of the paper by Dr Walker and colleagues¹ prompts us to make the following comments. We agree with Dr Walker that the conclusions of the study should be confined to the specific clinical setting and should not be extended to encompass the view that it is never harmful to stop atenolol abruptly in patients with coronary artery disease.

Walker *et al* saw no serious coronary events in 20 patients with stable angina in the six days after atenolol was stopped. This is not surprising because few would regard the risk of serious consequences from abrupt β blocker withdrawal as being high under these circumstances. They also noted no rebound in heart rate or blood pressure measured daily—this is also not surprising because these variables were recorded under unstressed conditions (which is why the earlier formal investigations into the phenomenon produced negative results). Furthermore, they saw no rebound in the consequences of treadmill exercise testing five days after atenolol was stopped—again this is not unexpected since these tests were probably on the late side and treadmill exercise is not the only form, and not necessarily the most potent form, of sympathetic stimulation to which patients may be exposed. These negative findings certainly do not demonstrate that the phenomenon of β adrenergic hypersensitivity is absent after treatment with atenolol has been stopped, nor that it would be safe to ignore the possibility of this consequence in clinical practice.

The manifestation of increased β adrenergic sensitivity as it gradually declines after the end of β blocker treatment will depend upon the net level of β adrenoceptor stimulation, and this in turn will depend upon the competition between sympathetic drive and the declining concentration of the β blocking drug. Our data showed that the phenomenon is indeed present after atenolol is stopped; under the particular circumstances of our study (in which heart rate was measured when the patient was standing after sublingual glyceryl trinitrate) the rebound was significantly greater for the group as a whole only at four days and not at five days. It occurred 2-3 days after propranolol, oxprenolol, "slow release" oxprenolol, and acebutolol.^{2,3} Exercise, moreover, is only one way of increasing sympathetic drive, and the increased sympathetic drive

with exercise is only one component cause of the increase in heart rate and myocardial energy requirements. Emotional stress, the reflex response to vasodilator drugs, or operation, can all cause very high β adrenergic activity and it would not be wise to regard this as always being innocent.

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This letter was shown to Dr Walker, who replies as follows:

Sir,

I thank Dr Lewis and Dr Henderson for their comments and share their concern that the results of our study¹ should not be extrapolated too widely—certainly not towards the extreme view they fear might be adopted. Our own views remain those condensed in the final paragraph of our paper.

While I agree that, on previous evidence, the risk of serious consequences from abrupt atenolol withdrawal was very small (otherwise we should not have performed our study), we believed that more than just a few clinicians were still anxious about what to expect in patients with stable coronary artery disease. I disagree that for patients with severe angina a hospital admission for coronary arteriography and a discussion of its implications, two maximal exercise tests, and the other investigations described consti-



tuted a period free of physical and emotional stress; however, as with previous similar studies^{2,3} no rebound effects or events were seen. As to whether exercise testing five days after atenolol withdrawal was too late to be influenced by adrenergic hypersensitivity, I refer Dr Lewis and Dr Henderson to their own paper in which they stated that "the peak rebound was reached at five (range four to seven) days after atenolol".⁴ Inspection of their fig 2a shows that an exaggerated heart rate response to standing with vasodilatation—which was "significant" only on day four—also appears to have been in evidence as late as day six. I agree that the heart rate response during exercise is only partly determined by sympathetic drive, and we did not claim to have demonstrated absence of increased drive on day five; but rather that the threshold for myocardial ischaemia during physical activity did not appear to be influenced by it.

Concerning possible extrapolations from our results, we limited our speculation to the contention that, since abrupt atenolol withdrawal in patients with severe stable angina resulted in a gradual and uneventful disappearance of β blockade, then in patients with mild or no symptoms a similarly uneventful outcome might be expected. Whereas to our knowledge this hope has not been disappointed in clinical practice, it seems fair to suggest that unduly wide extrapolations about the clinical importance of rebound hypersensitivity have been made by some,⁵ but certainly not all,⁴ workers who have succeeded in demonstrating this phenomenon in the laboratory. The rebound overshoot in heart rate response to standing with vasodilatation found after atenolol withdrawal by Ross *et al* appears to have averaged about 13 beats per minute.⁴ As we discussed, however, one consequence of atenolol withdrawal was that the heart rate at which myocardial ischaemia (angina and ST depression) became apparent during exercise was re-set upwards by as much as 35 (average 19) beats per minute.

Thus it does not follow that relatively small increases in heart rate (or sympathetic responsiveness or both) consequent upon β blockade withdrawal will necessarily promote myocardial ischaemia, let alone provide the trigger for catastrophic coronary events. Speculation about the possible effect of vasodilators or operation during withdrawal seems unnecessary for most patients in whom withdrawal of treatment is regarded as appropriate.

As long as there are only a few firm data on its frequency and mechanisms the β blockade withdrawal syndrome will doubtless continue to invoke controversy. As always, the clinician must make his own extrapolations from available data when considering the discontinuation of any particular β blocker.

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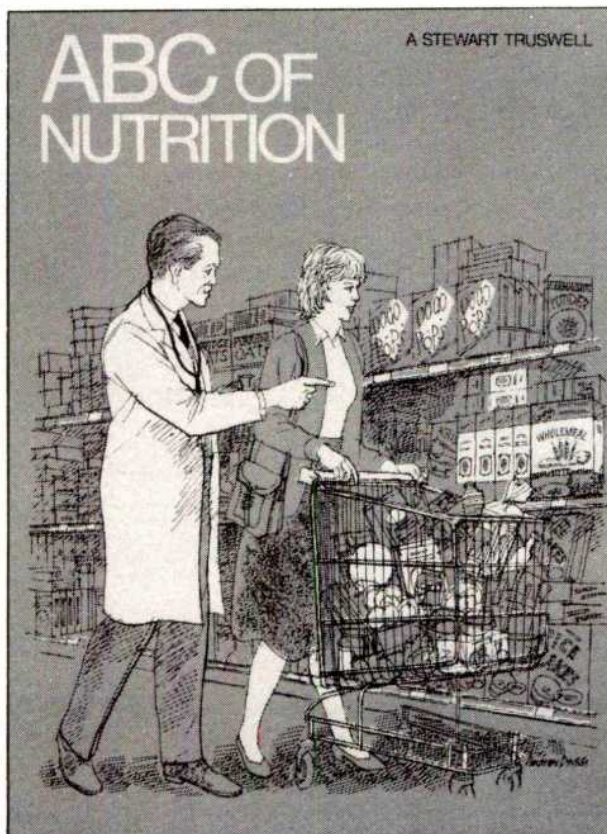
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Editorial: is atrial natriuretic peptide really a hormone? <i>R J Linden, M F Knapp</i>	299	Ventricular pacing improves exercise tolerance in patients with chronic heart block <i>M Papouchado, D W Pitcher</i>	366
The atrial natriuretic factor <i>J Genest</i>	302	Value of the bipolar lead CM5 in electrocardiography <i>A A Quyyumi, T Crake, L J Mockus, C A Wright, A F Rickards, K M Fox</i>	372
Isolated atrial amyloid contains atrial natriuretic peptide: a report of six cases <i>G C Kaye, M G Butler, A J d'Ardenne, S J Edmondson, A J Camm, G Slavin</i>	317	Case reports	
Cardiac abnormalities in familial palmoplantar keratosis <i>N Protonotarios, A Tsatsopoulou, P Patsourakos, D Alexopoulos, P Gezerlis, S Simitsis, G Scampardonis</i>	321	Angioplasty of an occluded left anterior descending coronary artery: usefulness of retrograde opacification of the distal part of the occluded vessel via the contralateral coronary artery in positioning the balloon catheter <i>G Grollier, Ph Commeau, J C Potier</i>	377
Left ventricular dysfunction in patients with angina pectoris and normal coronary angiograms <i>P M Schofield, N H Brooks, D H Bennett</i>	327	Congenital diverticulum of the heart arising from the coronary sinus <i>E Di Segni, A Siegal, M Katzenstein</i>	380
Assessment of regional left ventricular function by magnetic resonance <i>S R Underwood, R S O Rees, P E Savage, R H Klipstein, D N Firmin, K M Fox, P A Poole-Wilson, D B Longmore</i>	334	Left ventricular outflow tract obstruction due to anomalous mitral valve: successful mitral valve replacement in a four month old infant <i>P Morais, S Westaby, K A Hallidie-Smith</i>	385
Influence of a variant angina on the results of percutaneous transluminal coronary angioplasty <i>F Leisch, W Schützenberger, K Kerschner, W Herbinger</i>	341	Truncus arteriosus: successful surgical correction without the use of a valved conduit <i>K G Reid, M J Godman, J E Burns</i>	388
Nocturnal angina: precipitating factors in patients with coronary artery disease, and those with variant angina <i>A A Quyyumi, J Efthimiou, A Quyyumi, L J Mockus, S G Spiro, K M Fox</i>	346	Failure of Quintech Tx pacemaker caused by loss of stimulus-T interval shortening during exercise <i>T Fyfe, J F Robinson</i>	391
Syndrome X: the haemodynamic significance of ST segment depression <i>R D Levy, L M Shapiro, C Wright, L Mockus, K M Fox</i>	353	Correspondence	394
Exercise capacity and spontaneous heart rhythm after transvenous fulguration of atrioventricular conduction <i>P M Schofield, R J Bowes, N Brooks, D H Bennett</i>	358	Notices	394
		British Medical Association	

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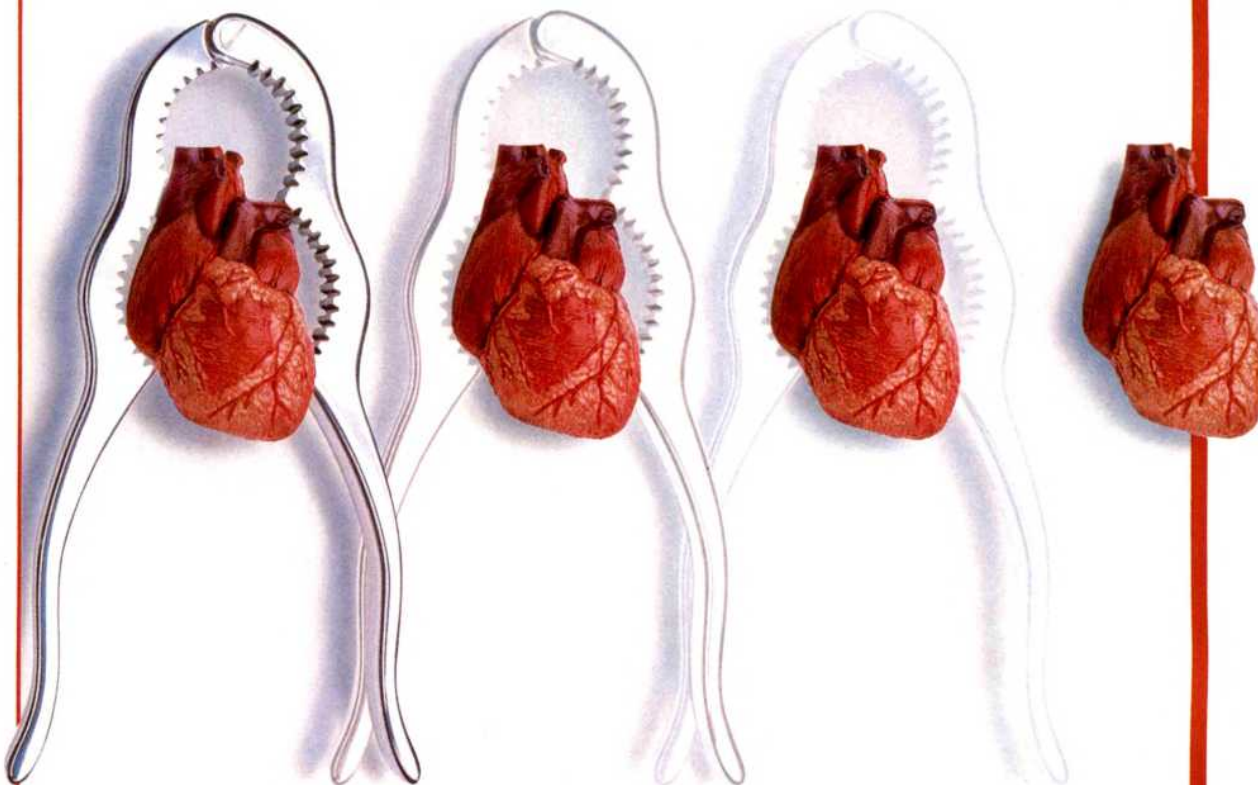
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Editorial

Is atrial natriuretic peptide really a hormone?

R J LINDEN, M F KNAPP

From the Department of Cardiovascular Studies, University of Leeds

Since the 1950s when granules were first observed histologically within the atrial wall there has been intense interest in their function. Two early key papers were those of Marie *et al*¹ and de Bold,² who showed that the granulation was related to the water/electrolyte balance, although a first time reader's starting point should be the meticulous histological investigation of Jamieson and Palade.³

On pages 302-16 of this issue of the *British Heart Journal* Genest gives an excellent historical account of this exciting research, much of which has been conducted at the Clinical Research Institute of Montreal.

There has been remarkably rapid progress in biochemical knowledge about atrial natriuretic peptides and perhaps now is the time to pause and take stock of the evidence about their postulated physiological functions.

Because in humans and in rats the atrial natriuretic factor is elaborated and localised in the granules of the atrial cardiocytes and is released in the blood, it is suggested that the atrial natriuretic factor is "a true circulatory hormone".⁴ But is there any evidence for the usual process of secretion from the atrial muscle cell? Certainly there is no evidence that the plasma concentrations attained during applied physiological stimuli (such as stretch of left atrial wall) can evoke acute responses. There is only evidence that large doses or large infusions that produce pharmacological concentrations of atrial natriuretic peptide have effects on the blood vessels (arteries, arterioles, veins), causing relaxation, particularly of pre-contracted muscle, and on the kidneys, causing natriuresis and diuresis.

Little is yet known of the biosynthesis and processing of atrial natriuretic peptide in, and its release from, the cardiocytes. Interpretation of the observed changes in granulation in relation to changes in fluid balance^{1,2} is at present difficult in view of studies^{5,6}

which suggest that granulation is dependent on release rather than synthesis, with low granularity apparently indicating high biosynthesis and turnover; also, in cultured cardiocytes there was an inverse relation between granulation and release of atrial natriuretic peptide.⁷ It seems likely, however, that in some circumstances low granularity will be associated with low biosynthesis. Exocytosis has not been seen despite specific attempts to detect it in several electron microscope studies,^{3,7} so it is still not certain that the cardiocytes secrete atrial natriuretic peptides by mechanisms analogous to those found in established endocrine organs. Low molecular weight forms are, however, found in plasma and again controversy is rife, evidence being presented both for the release of the high molecular weight form, for the later cleavage in plasma,^{8,9} and for the release of the low molecular weight form.¹⁰

Few studies have considered quantitatively the problem of the possible physiological stimuli for release and in these no evidence has been provided of a causative relation between stimuli within the physiological range, a rise in the plasma concentration of atrial natriuretic peptide, and the response of natriuresis and diuresis. For instance, the secretion of atrial natriuretic peptide and a causative relation have been implied¹¹ in the diuresis and natriuresis arising from stimulation of receptors in the atria—the so-called volume receptors.¹² Stimulation of atrial receptors is known reflexly to cause a water diuresis and small natriuresis¹³ but afferent nerves in the vagi are necessary for these responses to occur. When a large balloon was distended in the left atrium of anaesthetised¹⁴ or unanaesthetised dogs¹⁵ to stretch it and raise left atrial pressure to the top end of the pressure range in this animal (12-15 mm Hg) the plasma concentration of atrial natriuretic peptide increased by about 24 and 80 fmol/ml respectively (60 and 200 pg/ml, assuming $M_r = 2.5$ K daltons), with increases of the same magnitude whether or not the hearts were innervated. Knapp *et al*, however, obtained no natriuresis

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when this intervention was performed after atrial receptor denervation,¹⁶ indicating that the diuresis and natriuresis resulting from stimulation of atrial receptors¹⁷ were *not* caused by atrial natriuretic peptide. We suggested that such evidence must call seriously into question the claim that atrial natriuretic peptides are released into plasma in sufficient concentration for natriuresis to be a normal physiological function of these substances.

These investigations also support the contention that the plasma concentrations of atrial natriuretic peptide that evoke responses after infusion are much higher than those attained by stretching the atria or in disease. Normal endogenous basal concentrations of atrial natriuretic peptide are reported to be below 40 fmol/ml (100 pg/ml)^{14 15 18 19} and raised concentrations after intervention or in pathological conditions are generally < 200 fmol/ml.^{14 15 18-23} Even grossly unphysiological volume expansions of 30–40% of blood volume produced increases of only 4, 11, and 100 fmol/ml respectively.^{18 24 25}

From the evidence of Goetz¹⁵ it is possible to put the data from infusions of atrial natriuretic peptide into the context of these very low endogenous levels. Goetz reported plasma atrial natriuretic peptide concentrations of 170 and 300 fmol/ml in conscious dogs after infusions of atriopeptin III of 10.3 and 20.6 pmol/kg/min respectively¹⁵; thus infusions as low as 10.3 pmol/kg/min (25.8 ng/kg/min) would give plasma concentrations of far in excess of most of the reported endogenous concentrations. Yet Goetz reported no natriuresis or diuresis at these concentrations¹⁵; he found that a minimum infusion rate of 412 pmol/kg/min (1030 ng/kg/min) was necessary to produce natriuresis. Similar analysis of infusions in man leads to comparable values with infusions of about 50 ng/kg/min resulting in plasma concentrations of atrial natriuretic peptide^{21 26 27} in the pathological range. Very few published reports used infusion rates as low as those of Goetz¹⁵; most reports of the effects of atrial natriuretic peptide used doses within the pharmacological range and are thus unlikely to be useful in elucidating its physiological function.

The use of various high levels of infusion probably goes some way to explain the many contradictions that have emerged about the postulated functions and mechanisms of action of atrial natriuretic peptide, and these are exacerbated by the fact that most reviewers in discussing mechanisms of action still include early studies in which impure atrial extracts were used. These controversies include: disagreements about the site or sites of action in the kidney²⁸⁻³¹; the apparent paradox of in vitro vasodilatation and in vivo falls in blood pressure with the findings in vivo of an increase in peripheral

resistance,³² for which the current explanations are falling cardiac output and changes in capacitance³²; the finding that vascular selectivity is only partly related to vascular receptor binding³³; that the vascular effects are endothelium independent in contrast with other hormonal vasodilators³³; and the dissociation of excretion of sodium from the levels of cyclic guanosine monophosphate in plasma and urine.²⁸ The fact that high concentrations of atrial natriuretic peptide are found in patients with severe heart failure²² but are not associated with diuresis and natriuresis leads to claims that such patients may be resistant to the renal effects of endogenous atrial natriuretic peptide or that other factors (for example the renin-angiotensin-aldosterone system) may counteract the polyuric action of atrial natriuretic peptide in cardiac failure. But the high concentrations of the peptide could be incidental.

The excitement created by the discovery of atrial natriuretic peptides is understandable. The search for the postulated natural natriuretic substance has continued relentlessly for decades; and ever since the early experiments of Henry *et al* in 1956 in which they showed that distension of the left atrium by a balloon results in diuresis,³⁴ the atria have been seen as being important in fluid regulation. The possibility of tying these two strands together has been too much for the theorists.^{11 35} That alterations in fluid balance result in changes in atrial natriuretic peptide both in the atria and plasma is not in dispute and it does suggest a role that is linked with volume regulation. The suggestion that atrial stretch alone, that is without nerves being involved, is an adequate stimulus to raise the plasma concentration sufficiently to evoke responses, however, has not yet been demonstrated. It is difficult to understand how this postulated system of control of fluid balance may be working; stretching that causes leakage of atrial natriuretic peptide from atrial muscle seems an unlikely stimulus for a complex hormonal system that controls blood volume. At present it is impossible to determine whether the concomitant changes in atrial natriuretic peptide and fluid balance indicate a role in control of fluid homeostasis or whether the observed changes are secondary to fluid imbalance. The reported changes in endogenous concentrations appear to be too small to be important in short term control but it is possible that in the long term small but prolonged changes in the concentration of atrial natriuretic peptide have a role in the control of body sodium—a hypothesis that it may be too difficult to test.

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The atrial natriuretic factor

JACQUES GENEST

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Based on the Thomas Lewis Lecture delivered to the Autumn meeting of the British Cardiac Society, London, on 27 November 1985.

SUMMARY In less than three years since the rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats was reported the factor responsible for the diuretic, natriuretic, and vasodilating activity of the atrial homogenates was isolated, its chemical structure elucidated, and its total synthesis achieved. Also the cDNA and the gene encoding for the atrial natriuretic factor in mice, rats, and man have been cloned and the chromosomal site identified. The major effects of this hormone are vasodilatation, prevention and inhibition of the contraction induced by noradrenaline and angiotensin II, diuresis, and natriuresis associated in most instances with a pronounced increase in glomerular filtration rate and filtration fraction, inhibition of aldosterone secretion, and considerable stimulation of particulate guanylate cyclase activity. High density specific binding sites have been demonstrated in the zona glomerulosa of the adrenal cortex, in the renal glomeruli, and in the collecting ducts, and in the brain areas involved in the regulation of blood pressure and of sodium and water (AV3V region, subfornical organ, nucleus tractus solitarius, area postrema).

In proposing a new concept for the organisation of modern medical research and in setting up the Clinical Research Institute of Montreal, I have been greatly inspired by the outstanding group of American physicians at the turn of the century, such as Welch, Barker, and Longcope at Hopkins; Rufus Cole at the Rockefeller Institute; William Pepper and AN Richards in Philadelphia; and Folin and Peabody in Boston, among many others, but I owe to Sir Thomas Lewis the inspiration in articulating my own observations and transferring them into what is now the Clinical Research Institute of Montreal.^{1,2} The philosophy and thoughts of Sir Thomas Lewis have been expressed in a collection of addresses published under the title of *Research in Medicine* by HK Lewis of London in 1938. This small book is now a collector's item and contains four major addresses of Sir Thomas Lewis on clinical research, all of them published in the *British Medical Journal* in 1930, 1932, 1933, and 1935.

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Atrial natriuretic factor illustrates the great benefits of institutes in which daily interaction between researchers with various types of expertise is possible. This I believe accounts for the rapid progress in our understanding of the atrial natriuretic factor. In barely three years since its isolation it has been sequenced in our laboratories in June 1983; totally synthesised by Nutt and co-workers in August 1983; the cDNA and of the gene encoding for the atrial natriuretic factor have been cloned; its chromosomal location has been identified; its effects in experimental hypertension, on vascular smooth muscle, on renal function, aldosterone and vasopressin secretion have been investigated; receptors have been found in various tissues including the brain, the adrenal cortex, the kidneys, and ciliary bodies; and the messenger of its cellular activity has been identified.³

In 1981 de Bold *et al* reported the crucial observation of a striking diuretic and natriuretic activity when homogenates from rat atria were administered intravenously to control rats.⁴ Because of my lifelong interest in the factors regulating sodium as they relate to hypertension and because of Cantin's work in the past 15 years on atrial cardiocytes, our group

immediately realised the importance of de Bold's observation—hence the major effort we have made in this field.

Historical data

Kisch first described the presence of granules in the atrial cardiocytes of guinea pigs.⁵ They are adjacent to one or occasionally to both poles of the nucleus of the cardiocyte and are interspersed among the elements of a voluminous Golgi complex (fig 1). Jamieson and Palade demonstrated that such granules are present in cardiocytes of the atria of all mammals, including man,⁶ and Cantin and his group showed that these granules incorporated both [³H]-leucine and [³H]-fucose and that protein synthesis took place in the Golgi complex.^{7,8} In 1976, Hatt's group demonstrated that the degree of granularity in these atrial cardiocytes varied with the water and sodium intake⁹ (table 1).

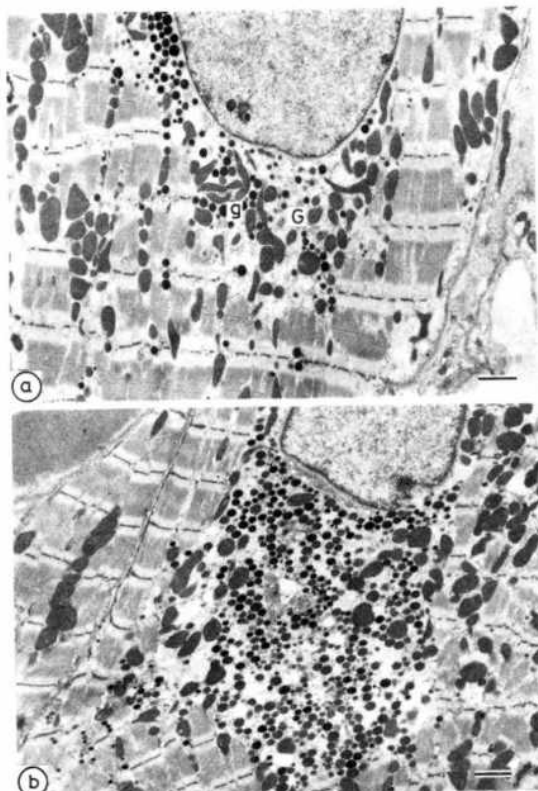


Fig 1 (a) Electronmicrograph of a granular cardiocyte showing the myofibrils, a well developed Golgi apparatus (G), and the granules (g). (b) Electronmicrograph of an atrial cardiocyte of a rat on a sodium free diet for 30 days showing a great increase in granularity.

Table 1 Specific granules expressed as a percentage of cell volume in atrial cardiocytes of rats⁹

Group	Right atrium	Left atrium
(1) Controls on standard diet	2.92 (p < 0.01)	1.11
(2) Total water restriction for 5 days	4.14*	1.77
(3) Total sodium restriction for 3 weeks	3.63	3.75‡
(4) Sodium load (1 g/dl sodium chloride as drinking fluid for 3 weeks)	1.40*	1.59
(5) Same as group 4 plus DOCA implant (25 mg for 3 weeks)	0.76†	1.19

*p < 0.05; †p < 0.005; ‡p < 0.01 compared with control group.
DOCA, desoxycorticosterone acetate.

Isolation and structure

Several active short peptides (21–33 amino acids) were isolated by different groups (fig 2).^{10–20} All of them contained the same sequence of 21 amino acids (Ser 103–Arg 125) with a cysteine–cysteine disulphide bridge. The differences in the active peptides isolated are caused by variations in the extraction and purification procedures and the choice of protease and peptidase inhibitors. Isolation and sequencing of larger peptides (up to 106 amino acids) showed that they all came from a common precursor.^{10–14} Synthetic deoxyoligonucleotides based on the amino acid sequence were used to clone the cDNA. This, in turn showed the structure of the pre-propeptide, which in rats is 152 amino acids long with two Arg-Arg residues of the carboxyl terminal, whereas the human pre-propeptide is made up of 151 amino acids without the two basic residues at the carboxyl terminal (fig 3).

The genes encoding for the atrial natriuretic factor in the rat and man have been cloned.^{21–33} The human gene has a span of 2 kb and consists of three coding blocks (exons) and two short introns of 122 and 1050 base pairs. The first exon codes for the signal peptide of 25 amino acids and the first 16 amino acids of the pro-hormone. The second exon codes for most of the pro-hormone from amino acids 41 to 150, including the atrial natriuretic factor, and the third exon encodes the last amino acid 151 Tyr or in the case of the rats, the last three amino acids Tyr 150, Arg 151, and Arg 152, which do not appear to be important for the biological activity of the atrial natriuretic factor.

Yang-Feng *et al.*, in collaboration with Drouin and Nemer from the Clinical Research Institute of Montreal, demonstrated that the atrial natriuretic factor gene is located on the distal short arm of chromosome 1 in man and on chromosome 4 in mice.³⁴

Circulating form of atrial natriuretic factor

In man the 28 amino acid sequence Ser 99-Tyr 126 was isolated from atrial homogenates by Kangawa and Matsuo³⁵ and by Thibault *et al.*^{35a} It differs from the rat atrial natriuretic factor by having methionine instead of isoleucine in position 110 (fig 4). Although it has not yet been sequenced from human plasma, on reverse phase high performance liquid chromatography the peptide isolated behaves identically with the 28 amino acid sequence of Ser 99-Tyr 126.³⁵

The circulating form of the atrial natriuretic factor was isolated from plasma of morphine treated rats (morphine (10 mg/rat) increased circulating atrial natriuretic factor 40–50 times)³⁶ and from the perfused rat heart by the Langendorf technique after extraction with Vycor glass beads, immunoaffinity chromatography on Sepharose 4-B anti-atrial natriuretic factor, and reverse phase high performance liquid chromatography. It has been sequenced and shown to be the 28 amino acid peptide Ser 99-Tyr 126.^{37,38} Schwartz *et al* reported similar findings.³⁹

Structure activity relation

The structure activity relation of various atrial natriuretic factor peptides was studied by comparison with the synthetic atrial natriuretic factor made up of 26 amino acids (Arg 101-Tyr 126). The shorter peptides were obtained by sequential cleavage at the amino terminal by Edman degradation (amino acids 101, 102, 103, 104, to 105) or by the use of various carboxypeptidases at the carboxyl terminal (amino acids 122, 123, 124, 125, to 126).^{40,40a,41} The resulting shorter forms produced were all identified by amino acid analysis and sequencing. The biological activity of these shorter forms was compared with the 26 amino acids from Arg 101 to Tyr 126 in several systems: in vivo rat assay for diuresis and natriuresis; in vitro relaxation of strips of aorta and chick rectum, inhibition of aldosterone secretion from beef and rat zona glomerulosa cell cultures, specific binding to mesenteric artery smooth muscle membranes and to beef zona glomerulosa cell membranes.^{40–42} The 26 amino acid sequence Arg 101-Tyr 126 was found to be the most potent in these assays. The removal of Phe 124, Arg

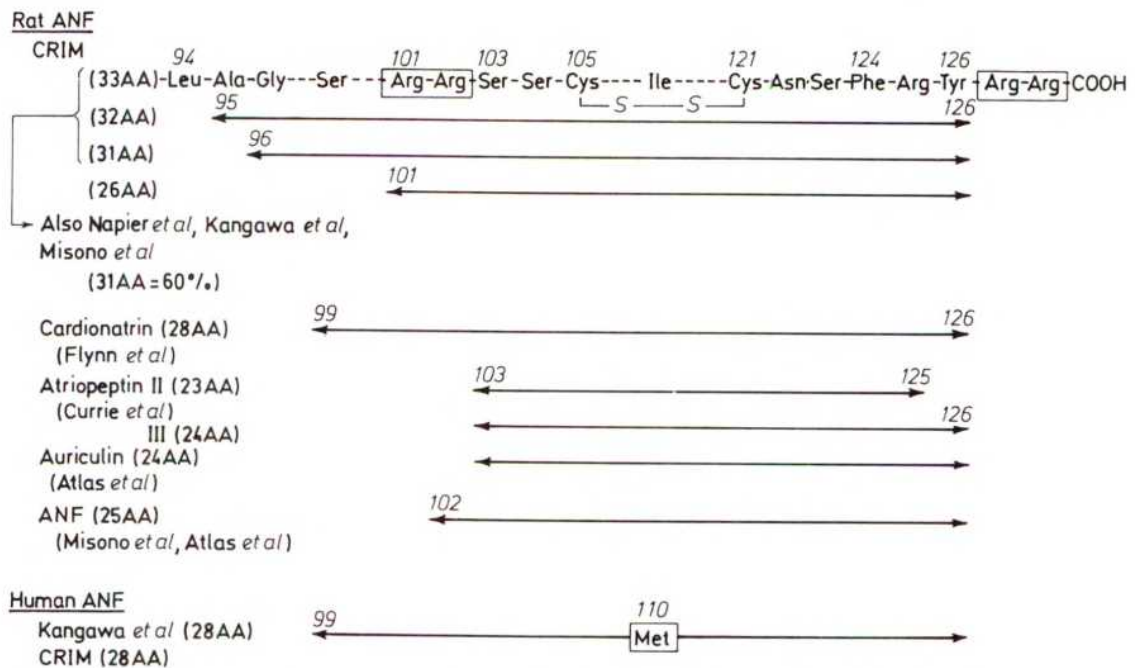


Fig 2 Isolated forms of low molecular weight atrial natriuretic factor with diuretic, natriuretic, and vasorelaxant properties. Numbers above the amino acids are the international classification. The short active forms were all isolated from the carboxyl terminal. The names given to some low molecular weight peptides are shown. Atriopeptin I, which is made up of 21 amino acids, is not shown because of its very low potency. The isolation of human atrial natriuretic factor by Kangawa *et al*²² was soon confirmed by the group at the Clinical Research Institute of Montreal.^{35a} (Reproduced with the permission of Endocrine Reviews.)

125, and Tyr 126 considerably decreased the biological activities of the atrial natriuretic factor, whereas the removal of amino acids 101, 102, 103, 104 had much less effect (table 2).

The 26 amino acid peptide Arg 101-Tyr 126 was found to be as potent and as active as the 28 amino acid peptide Ser 99-Tyr 126 in all assays used.^{40 40a}

The 26 amino acid peptide (Arg 101-Tyr 126) was sequenced in our laboratories in June 1983 and it was synthesised in August 1983 by Nutt *et al.*^{42a} This factor has been used in all the studies performed by our group and many others have used it too.

Effects of atrial natriuretic factor on the heart and haemodynamic function

Bolus injections of synthetic atriopeptin III (24 amino acids, Ser 103-Tyr 126) significantly reduced cardiac output in anaesthetised dogs and rats.^{43 44} Similar results were obtained with atriopeptin II (23 amino acids Ser 103-Arg 125).⁴⁵ On the other hand, in open chest anaesthetised dogs infusions of the atrial natriuretic factor (26 amino acids Arg 101-Tyr 126) did not significantly alter cardiac output or contractility (left ventricular dp/dt max).⁴⁶ The atrial

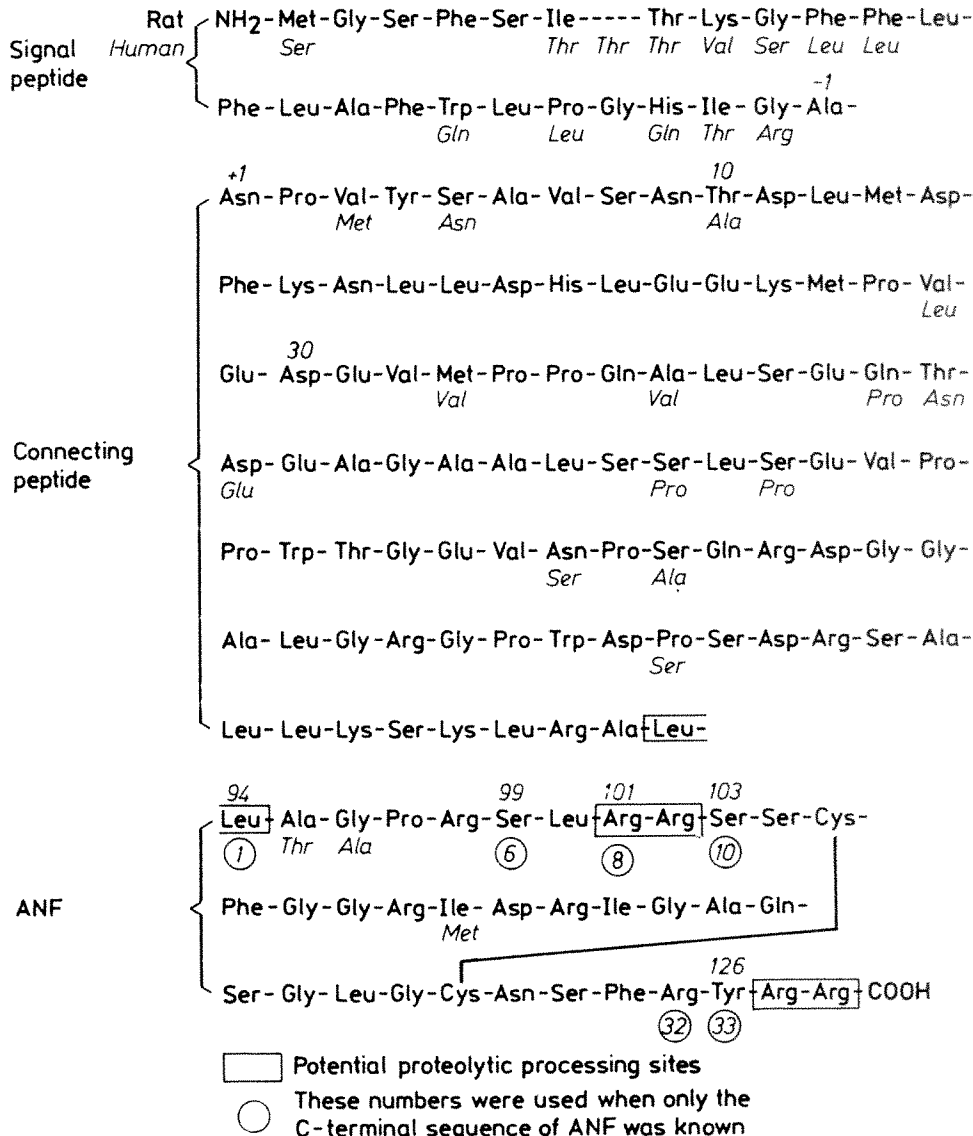


Fig 3 Amino acid sequence of the atrial natriuretic factor (ANF) pre-propeptide in man and in rats. (Reproduced with permission of Endocrine Reviews and of Zivin *et al.*²¹ and Nemer *et al.*³⁰.)

natriuretic factor has no inotropic effect (R Tarazi, personal communication).

The atrial natriuretic factor content of atrial tissue is significantly lower in the B10 14 6 strain of hamsters with a hereditary form of cardiomyopathy and severe congestive heart failure than in control age matched animals.^{47 48} The most striking finding is the significant increase in mean circulating plasma immunoreactive atrial natriuretic factor at all stages

of congestive heart failure from 25.6 (1.4) pg/ml in control hamsters to 236 (57) pg/ml. Blood pressure is always lower in these hamsters than in the controls. These findings suggest that the decreased amounts of atrial natriuretic factor found in atrial tissue are the result of depletion and that sodium retention and oedema would probably occur earlier if the atrial natriuretic factor had not already been secreted in large amounts. Infusions of the atrial natriuretic factor through Alzet minipumps at 30 pmol/kg/min for seven days to hamsters with congestive heart failure significantly reduced heart weight.

Significantly increased blood concentrations of immunoreactive atrial natriuretic factor have been reported in patients with paroxysmal tachycardia⁴⁸⁻⁵⁰ and in patients with congestive heart failure.^{51 52} In patients with various valvar or cardiomyopathic diseases there was a strongly significant correlation between plasma atrial natriuretic factor concentrations and left ventricular filling pressure,^{51 52} which strongly supported experimental data that suggested that atrial stretch is probably the major stimulus for the release of atrial natriuretic factor.^{53 54} Plasma immunoreactive atrial natriuretic factor concentrations were significantly higher in almost all patients with valvar disease, especially of the mitral valve.

In a study of 110 consecutive patients undergoing diagnostic coronary angiography for coronary heart disease mean (SD) plasma concentrations of immunoreactive atrial natriuretic factor were significantly

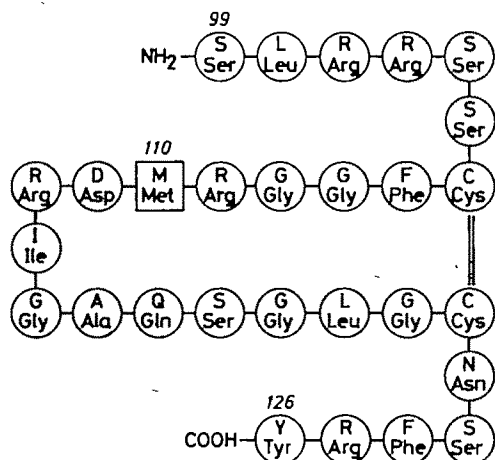


Fig 4 Amino acid sequence of human atrial natriuretic factor which is the same as that of the rat, except that in the latter the amino acid in position 110 is an isoleucine instead of a methionine. (Reproduced with the permission of *Endocrine Reviews*.)

Table 2 Relative potency of rat atrial natriuretic factor peptides

Atrial natriuretic factor	Natriuresis	Relaxation		Binding to bovine adrenal capsules	Inhibition of aldosterone secretion
		Chick rectum	Rabbit aorta		
Gly96-Tyr126 (31 amino acids)	+++	—	++	++++	++++
N terminal					
Arg 101-Tyr 126	++++	++++	++++	++++	++++
Arg 102-Tyr 126	++++	+++	++++	++++	++++
Ser 103-Tyr 126	++++	++	+++	+++	++++
(Atriopeptin III-auriculn)					
Ser 104-Tyr 126	++++	++++	+++	+++	+++
Cys 105-Tyr 126	++++	++++	++++	+++	+++
COOH terminal					
Arg 101-Arg 125	++++	++++	+++	++++	++++
Arg 101-Phe 125	+++	—	++	++	—
Arg 101-Ser 123	++	+++	++	++	++
Arg 101-Cys 121	+	++	++	+	+
Atriopeptin I Ser 103-Ser 123	++	+	++	+	+
Atriopeptin II Ser 103-Arg 125	+++	+	++	+++	+++

++++, very active; +++, moderately active; ++, slightly active; +, minimally active.
Data from Garcia *et al.*,^{40 46a} Thibault *et al.*,⁴¹ and De Lean *et al.*⁴²

higher in patients with a reduction $\geq 70\%$ in coronary lumen diameter than in patients with atypical chest pains and normal coronary anatomy (121 (55) pg/ml vs 102 (37); $p < 0.01$).⁵⁵ Patients with a left ventricular end diastolic pressure > 14 mm Hg or with an ejection fraction of < 0.5 have significantly higher plasma concentrations of immunoreactive-atrial natriuretic factor (table 3).

Table 3 Mean (SD) plasma concentrations of immunoreactive atrial natriuretic hormone (IR-ANF)* in 110 consecutive patients with coronary heart disease⁵⁵

Group	IR-ANF (pg/ml)	p
Values in patients with normal coronary arteries	102 (37)	< 0.01
Values in patients with 70% reduction in coronary diameter	131 (55)	
Left ventricular end diastolic pressure		< 0.0001
< 14 mm Hg (No 53)	109 (35)	
> 14 mm Hg (No 45)	148 (60)	< 0.001
Ejection fraction:		
> 0.5 (No = 81)	119 (44)	< 0.001
< 0.5 (No = 17)	1645 (70)	

*Direct RIA

Effects of atrial natriuretic factor on the kidney

The major effect of the atrial natriuretic factor is a rapid (within 3–5 min), massive, and short (< 20 min) diuresis (5–20 fold) and natriuresis (5 to 50 fold) in rats, dogs, monkeys, and man.^{56–62} It also increases, to varying degrees, excretion of potassium, calcium, magnesium, and phosphate. The natriuretic response was 5–7-fold greater when the atrial natriuretic factor was administered during a pressor infusion of angiotensin II⁶³ and was greatly decreased in rats with atrial appendectomy.^{64,65} All the atrial natriuretic factor peptides isolated from Leu 94-Ser 103 to Tyr 126 have the same effects on the kidney, albeit in different degrees. In most studies in rats and man intravenous atrial natriuretic factor considerably increases glomerular filtration rate, filtration fraction, urine volume, and sodium excretion (table 4). Renin secretion is usually inhibited.^{58,66,67} In some studies and at lower doses,^{57,68–70} the atrial natriuretic factor does not have any effect on the glomerular filtration rate. Considerable diuresis and natriuresis were obtained without any change in glomerular filtration rate when infusions of atrial natriuretic factor were given to dogs under severe sodium restriction⁷¹ and to rats on a low protein (8%) diet.⁷²

From all studies done so far, it appears that the major factor involved in the diuresis and natriuresis is the increase in glomerular filtration rate and filtration fraction. Nevertheless, there must be a

tubular effect. The evidence available so far does not accord with a proximal tubular effect. Autoradiography did not show specific binding of ¹²⁵I-atrial natriuretic factor in the proximal tubules⁷³; no receptors were demonstrated by specific binding studies in the proximal tubules⁷⁴; and when atrial natriuretic factor was added to pure preparations of dog proximal tubules there was no change in cyclic guanosine monophosphate or in particulate adenylate cyclase activity.⁷⁵ Atrial natriuretic factor had no effect on glutamine, lactate, glucose, and oxygen uptake or on glucose or lactate production^{76,77}; on the other hand, Kohashi *et al* have recently shown that succinate stimulated oxygen consumption was inhibited when rat's kidney slices were incubated with the atrial natriuretic factor Ser 103-Tyr 126.⁷⁸ Atrial natriuretic factor had no detectable effect on the transepithelial potential and on volume absorption in the perfused isolated rabbit proximal tubules, either when the atrial natriuretic factor was added to the bath or was infused in the luminal perfusate.⁷⁹

High density binding sites for ¹²⁵I labelled atrial natriuretic factor were found in the glomeruli by radioautography,^{80,81} and Bianchi *et al* have recently demonstrated that most atrial natriuretic factor binding sites are found on the podocytes of the epithelial cells of the glomeruli⁸⁰ (fig 5). Silver staining of the glomeruli was abolished when an excess of cold atrial natriuretic factor was given simultaneously with the labelled atrial natriuretic factor. In contrast 60% of the binding sites for ¹²⁵I-angiotensin II are located over mesangial cells.

Studies of free water clearance, stop-flow experiments, and micropuncture reported by Sonnenberg *et al*,⁸² Schnermann's group,⁸³ and Yakimura *et al*⁷⁰

Table 4 Renal response of dog to atrial natriuretic factor (ANF) (Arg 101-Tyr 126) infused into the renal artery⁵⁸

Variable	Control	ANF (0.3 µg/kg/min (45 min))
Mean arterial pressure (mm Hg)	123 (9)	118 (9)*
Renal blood flow (ml/min)	126 (8)	117 (8)†
Glomerular filtration rate (ml/min)	23.1 (3.5)	30.7 (1.9)†
Renal vascular resistance (mm Hg/ml/min)	0.99 (0.1)	1.04 (0.13)
Filtration fraction	0.19 (0.04)	0.27 (0.03)†
Fraction excreted of sodium filtered (%)	0.6 (0.2)	5.8 (0.8)†
Fraction excreted of lithium filtered (%)	32.2 (7.1)	60.3 (5.7)†
Fraction excreted of phosphate filtered (%)	8.7 (3.4)	41.6 (11.7)†
Renin secretion rate (ng/min)	296 (85)	17 (11)†

* $p < 0.05$; † $p < 0.01$, compared with control values
Values shown are mean (SD). Modified from Burnett *et al*⁵⁸

suggested an effect on the distal tubules or early collecting ducts. Autography showed the greatest number of silver grains in the inner medulla of the rat kidney in the collecting ducts; and far fewer were seen in the interstitial cells⁸¹ (table 5). The localisation of atrial natriuretic factor in the intercalated cells of the collecting ducts in rat kidney has been shown by immunohistochemical methods.⁸⁴⁻⁸⁵ The absence of any change in oxygen or in glucose use at the level of the collecting ducts suggests that the atrial natriuretic factor reduces sodium transport in the distal tubules by an unfamiliar mechanism (table 6).

Table 5 Ultrastructural localisation of silver grains in the renal medulla after injection of ¹²⁵I-labelled atrial natriuretic factor

Structure	Outer medulla		Inner medulla	
	No of grains	%	No of grains	%
Vasa recta	266	70	49	15
Thin loop of Henle	16	4	66	21
Thick loop of Henle	44	12	—	—
Interstitial cell	—	—	62	19
Collecting duct	52	14	143	45
Total	380	100	320	100

Table 6 Sites of action of added atrial natriuretic factor in various dog kidney preparations

Pure preparations	Radioligand binding	Adenylate cyclase inhibition	Particulate guanylate cyclase activation	Cyclic guanylate monophosphate levels (increase over basal (fold))	O ₂ consumption	Glucose utilisation	Rate of glycolysis
Proximal tubule	0	0	0	0	0	0	—
Loop of Henle	+	++	+	2	0	0	—
Collecting duct	+	+++	+	3	—	—	0
Glomerulus	+++	+++	+++	50	—	—	—

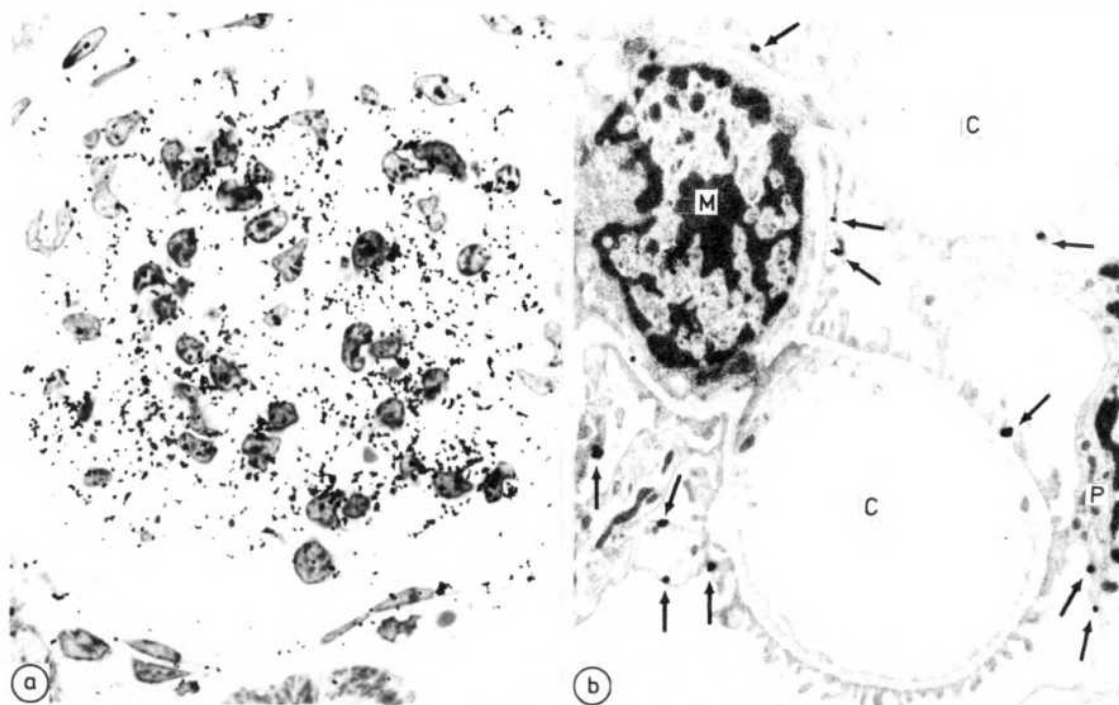


Fig 5 (a) Radioautograph of a semi-fine section of rat glomerulus post-stained with toluidine blue after injection of ¹²⁵I-labelled atrial natriuretic factor. The silver grains follow the contour of the glomerular capillaries and are located mostly over the epithelial cells. (b) Part of the glomerulus seen by electronmicroscopy after injection of ¹²⁵I-atrial natriuretic factor. Silver grains are localised over the podocytes (arrows) of epithelial visceral cells (P), mesangial cells (M), and capillary lumen (C).

In pure preparations of glomeruli over 80% of guanylate cyclase was found in the particulate form; the remainder was in the fractions containing either collecting ducts or thick loops of Henle. There was no detectable particulate guanylate cyclase activity in the proximal tubules.⁷⁵

Effects of the atrial natriuretic factor on vascular smooth muscle and in experimental hypertension

The atrial natriuretic factor was shown by Currie *et al.*¹⁸ by Garcia *et al.*⁸⁶ and by several other groups⁸⁷⁻⁹⁰ to have a direct vasorelaxing effect on vascular smooth muscle, especially on the renal artery but also in the aorta and the mesenteric arteries. The addition of atrial natriuretic factor to a bath containing strips of renal artery or of aorta from rat or rabbit inhibits and prevents the contractile effects of added noradrenaline or angiotensin II.

Schiffrin *et al.*⁹¹ and Winkvist^{90,92} studied the differences in the regional distribution of atrial natriuretic factor receptors in the rabbit vasculature. High affinity receptors were present in arteries and veins from different regions but there were more in arteries that responded well to low concentrations of atrial natriuretic factor, such as the renal artery, and less in tissues that were unresponsive to atrial natriuretic factor, such as the arteries of the ear and the femoral artery. The vasorelaxant selectivity of the atrial natriuretic factor, first suggested by Garcia *et al.*⁸⁶ has been confirmed by Cohen and Schenck⁹³ and by Faison *et al.*⁹⁴ in isolated rabbit arteries. The aorta and the renal, carotid, and mesenteric arteries are very responsive; the pulmonary, femoral, and iliac arteries less so; and the saphenous, basilar, and ear arteries are comparatively unresponsive. According to Winkvist,⁹² the vascular myogenic tone of the rabbit facial vein is probably the most sensitive bioassay for the atrial natriuretic factor. The arcuate arteries of the rat kidney were very sensitive to the vasorelaxing effects of the atrial natriuretic factor after activation with 40 mmol/l potassium salt solution, whereas small arteries from other territories (mesenteric, femoral, cerebral, and coronary) showed no response to the atrial natriuretic factor.⁹⁵

Garcia *et al.* made detailed studies of the effects of bolus injections or of continuous intravenous infusions of atrial natriuretic factor in rats with various types of hypertension.⁹⁶⁻⁹⁸ Bolus injections of atrial natriuretic factor (1 µg) to both two kidney-one clip and one kidney-one clip hypertensive rats reduced blood pressure to normal for 35 min to > 60 min. When the atrial natriuretic factor was infused intravenously at the rate of 1 µg/h continuously for 6 days to two kidney-one clip hypertensive rats, blood

pressure came down to normal (< 140 mm Hg systolic pressure) after the second day and remained so throughout the administration of atrial natriuretic factor (fig 6). At the end of this six day infusion period, both plasma renin activity and heart weight were significantly increased in the untreated two kidney-one clip hypertensive rats, whereas there was no change in plasma renin activity or in heart weight in those receiving atrial natriuretic factor infusions. Longer infusions (12 days) at lower doses (100 ng/h) produced the same results.

Continuous infusions of atrial natriuretic factor (100 ng/h) for six days in one kidney-clip hypertensive rats resulted in a fall in systolic pressure from a mean of 193 mm Hg systolic in the control period to 145 mm Hg after the third day of administration. The fall in blood pressure in rats receiving atrial natriuretic factor was accompanied by a significantly greater diuresis and natriuresis than that in similar untreated rats that had had sham operations or removal of one kidney.

Infusion of the atrial natriuretic factor at 100 ng/h for six days in spontaneously hypertensive rats (mean systolic pressure 177 mm Hg) reduced systolic blood pressure to 133 and 143 mm Hg on the fifth and sixth days of infusion respectively (fig 7).⁹⁸

Dahl's salt sensitive hypertensive rats had mean (SD) concentrations of plasma immunoreactive-atrial natriuretic factor that were three times higher

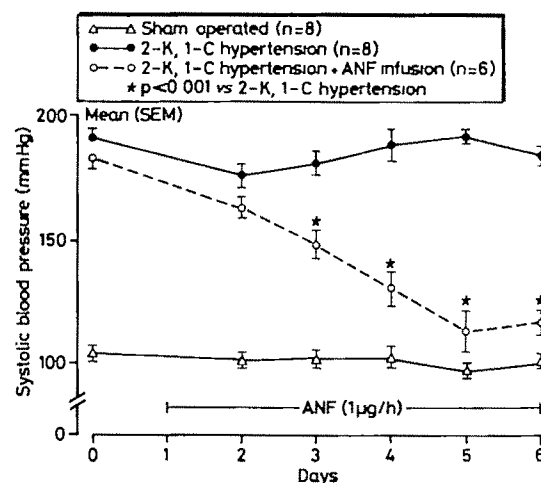


Fig 6 Effect of a chronic intravenous infusion of synthetic atrial natriuretic factor (ANF) 26 AA (Arg 101-Tyr 126) at 1 µg/h for 6 days by minipump in three groups of rats, one sham-operated, the second with two kidney-1 clip (2-K, 1-C) hypertension, and the third group similar to the second group but receiving the ANF infusion. (Reproduced with the permission of Proc Soc Exp Biol Med and of the authors.⁹⁷)

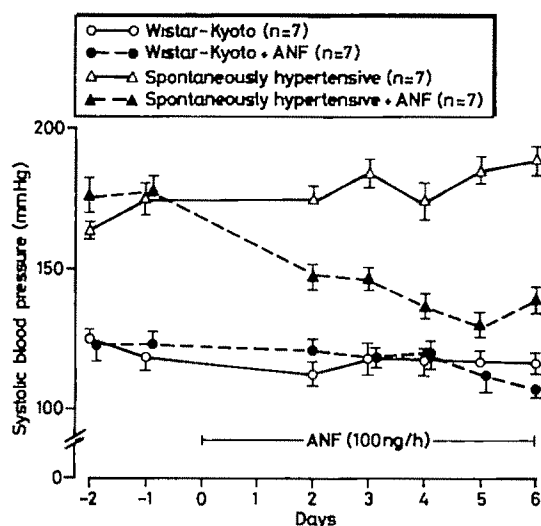


Fig 7 Effect of a chronic intravenous infusion of synthetic atrial natriuretic factor (ANF) 26 amino acid peptide (Arg 101-Tyr 126) at 100 ng/h through mini-pumps to Wistar-Kyoto control rats with or without ANF and to spontaneously hypertensive rats with or without ANF. (Reproduced with the permission of *Proc Soc Exp Biol Med* and of the authors.⁹⁸)

than those of the salt resistant rats (15 (54) pg/ml versus 52 (7), $p < 0.02$)⁹⁹ (J Gutkowska *et al.*, personal communication), but according to Hirata *et al.*¹⁰⁰ these animals show a considerably reduced natriuretic response to exogenously administered atrial natriuretic factor, possibly because of a reduced renal papillary plasma flow.⁹⁹ Ishihara *et al.* reported that intravenous injection of atrial natriuretic factor to deoxycorticosterone acetate-salt hypertensive rats reduced blood pressure considerably.⁶⁹ The atrial natriuretic factor inhibits the hypertension induced by chronic pressor infusions of noradrenaline in conscious rats whether it is administered before or during the hypertensive state induced by noradrenaline.¹⁰¹ These results indicate that the study of atrial natriuretic factor administration in hypertensive patients may be promising.

Effects of atrial natriuretic factor on adrenal cortex and brain

The atrial natriuretic factor significantly inhibits release of aldosterone both in cultures of beef and rat zona glomerulosa cells and in vivo in rats and man.¹⁰²⁻¹⁰⁸ There is an inhibitory effect not only on the basal secretion of aldosterone but also even more strongly in vitro when aldosterone release is stimulated by angiotensin II, corticotrophin, prostaglandin E₁, or forskolin (table 7).

Table 7 Inhibition by atrial natriuretic factor (ANF) (14 nmol/l) of aldosterone production in cultured bovine zona glomerulosa cells

	Control	ANF (pmol/well)	% inhibition
Basal	1.0 (0.1) (3)*	0.8 (0.2) (3)	20†
Ang II (10 nmol/l)	6.4 (0.5) (4)	3.7 (0.3) (4)	52‡
ACTH (10 nmol/l)	8.8 (0.4) (2)	5.3 (0.7) (2)	44‡
PGE ₁ (1 µmol/l)	12.4 (0.6) (2)	4.0 (0.2) (2)	72‡
Forskolin (1 nmol/l)	11.5 (0.7) (2)	7.0 (0.4) (2)	43‡

Values shown are mean (SEM).

*Number of replicate experiments.

† $p > 0.05$ vs control by two-way anova.

‡ $p < 0.01$ vs control by two-way anova.

ACTH, adrenocorticotrophin; PGE₁, prostaglandin E₁.

Binding of ¹²⁵I-labelled atrial natriuretic factor in the brains of rats and guinea pigs has been shown by means of an in vitro receptor radioautographic technique.¹⁰⁸ The distribution of binding sites for ¹²⁵I-atrial natriuretic factor in the brain was unique, with high density binding sites in the median eminence, the subfornical organ, area postrema, and the nucleus tractus solitarius, all areas known to be involved in the regulation of blood pressure and in renin dependent hypertension and in the regulation of water and sodium. Neurons that were immunoreactive to atrial natriuretic factor Ser103-Tyr126 were detected in the brain of rats, especially in the anteroventral region of the third ventricle (periventricular nucleus of the hypothalamus and pre-optic area).¹¹⁰⁻¹¹¹ Detectable concentrations of immunoreactive atrial natriuretic factor were found in homogenates of rat hypothalamus,^{112,85} in the posterior pituitary,¹¹³ in the ganglia nodosa of the vagus, and in the cervical sympathetic ganglion in the rat.¹¹⁴ In addition, high density binding sites were seen in the "pigmented" epithelium of the ciliary processes of the eyes both in rats and in rabbits.¹¹⁵

Plasma concentrations measured by radio-immunoassay in experimental and human hypertension

The mean (SD) concentration of immunoreactive atrial natriuretic factor in the plasma of conscious rats with catheters implanted in the jugular vein for 24 hours was 94 (17) pg/ml.³ Administration of morphine, ether, and ketamine to rats increased plasma concentrations of immunoreactive atrial natriuretic factor by 50, nine, and two times respectively.³⁶

Studies of spontaneously hypertensive rats at 16 weeks of age (systolic pressure 195 mm Hg) showed that the mean (SEM) plasma concentration of immunoreactive atrial natriuretic factor was 275 (24) pg/ml compared with 140 (22) pg/ml in

Wistar/Kyoto rats with systolic pressures of 116 mmHg.¹¹⁶ Although there was no difference in immunoreactive atrial natriuretic factor content of the right atrium, the immunoreactive atrial natriuretic factor content of the left atrial tissue was significantly lower in spontaneously hypertensive rats than in Wistar/Kyoto rats. This may be related to the significant increase in left atrial pressure found in the spontaneously hypertensive rats by Noresson *et al.*¹¹⁷ and would be consistent with many experimental studies suggesting that the atrial stretch or pressure is a major stimulant of the atrial natriuretic factor release.

Plasma concentrations of immunoreactive atrial natriuretic factor in patients with mild and moderate essential hypertension were measured by radioimmunoassay after purification on Sep-Pak cartridges (Millipore, Milford, MA, USA). The mean (SEM) plasma concentration of immunoreactive atrial natriuretic factor was 11.9 (1.0) pg/ml in 67 normotensive control subjects (mean age 34.7 and blood pressure 117/70 mm Hg), and 13.5 (1.5) pg/ml in 44 hypertensive patients (mean age 47 and blood pressure 158/94 mm Hg) (P Larochelle, JR Cusson, J Gutkowska, *et al.*, personal communication). This difference was not statistically significant. These results were confirmed recently by the group of Burnett *et al.*^{117a} They contrast with the slight but significant increase in plasma immunoreactive atrial natriuretic concentrations reported by Arendt *et al.*,¹¹⁸ by Sugawara *et al.*,¹¹⁹ and Sagnella *et al.*¹²⁰; the latter two groups used the same plasma purification procedure by Sep-Pak cartridges. These results may differ because of the nature of hypertension, its severity, and the presence of some degree of congestive heart failure in the groups studied. All our patients had a thorough evaluation, including renal arteriography, and had mild or moderate essential hypertension.

Nevertheless, intravenous bolus injections of 3, 12.5, and 25 µg of human atrial natriuretic factor had no effect on blood pressure in healthy subjects despite peak plasma concentrations of up to 1100 pg/ml (JR Cusson, P du Souich, LA Rochelle, *et al.*, personal communication). Nor did intravenous infusions of human atrial natriuretic factor of 3.2 µg/min for 30 min producing mean plasma concentrations of 230–280 pg/ml have any effect on blood pressure and systolic and diastolic pressures fell by 7 and 10 mm Hg respectively when 6.25 µg/min of atrial natriuretic factor was infused for 45 minutes (mean (SEM) plasma concentration 625 (87) pg/ml).¹²¹ These findings suggest that the atrial natriuretic factor does not reduce blood pressure unless plasma concentrations exceed 600 pg/ml.

On the other hand, several reports indicate

significant increases in right atrial pressure, pulmonary wedge pressure (reflecting left atrial pressure), and cardiothoracic volume in patients with essential hypertension^{122–124b} (table 8); these are all factors known to increase the release of the atrial natriuretic factor. These observations added to the fact that all reported measurements of plasma concentration of immunoreactive atrial natriuretic factor (after purification on Sep-Pak cartridges) were below 100 pg/ml in patients with mild and moderate essential hypertension strongly suggest that the atria were less responsive to increased right and left atrial pressures and cardiothoracic volume and hence released less atrial natriuretic factor (table 8).

Table 8 Central haemodynamics and hypertension

(1) Increase of left atrial pressure in spontaneous hypertension ¹¹⁷
(2) In patients with essential hypertension
(a) Increased right atrial pressure
Increased pulmonary wedge pressure
Increased cardiothoracic volume (CTV)
Increased CTV, total blood volume ¹²³
(b) Raised pulmonary systolic and diastolic arterial pressure

Such atrial hyporesponsiveness would be compatible with (a) Guyton's hypothesis¹²⁵ that the hypertensive kidney cannot excrete sodium loads, hence the increase in blood pressure to re-establish the sodium equilibrium, that is the "pressure natriuresis" demonstrated in rats by Tobian *et al.*^{126–128}; (b) the inappropriately high aldosterone secretion rate, plasma concentration, and excretion rate during periods of high sodium intake in patients with essential hypertension,^{129 130} which could be caused by decreased inhibition of aldosterone release owing to a deficient atrial natriuretic response; and (c) a decreased degree of vasorelaxation with predominant vasoconstriction resulting from an insufficient release of atrial natriuretic factor and an increased intracellular sodium concentration. This would lead to the increased vascular reactivity and resistance that are fundamental to the hypertensive process¹³¹ and would accompany the high concentrations of plasma Na⁺/K⁺ ATPase activity inhibitor reported in patients with essential hypertension.¹³²

Since the atrial natriuretic factor is a peptide and as such is degraded by the gastric juice when given orally, its application in clinical states (essential hypertension, hypertensive crises, congestive heart failure and other oedematous states, primary and secondary hyperaldosteronism) depends on the synthesis of analogues, probably non-peptidic, which will be absorbed and will be biologically active when given by mouth.

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Addendum

Normal plasma concentrations of immunoreactive atrial natriuretic factor have recently been reported in patients with untreated essential hypertension without left ventricular hypertrophy.

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Uses: For the prophylaxis of angina pectoris. Isosorbide mononitrate, the active constituent of Mono-Cedocard, is the major active metabolite of isosorbide dinitrate. It has significant vasodilator activity, the strongest effect being exerted on the venous system, and a lesser effect on the arterial circulation. As a consequence, the heart has less work to perform against diminished resistance, and therefore oxygen requirement is reduced. After oral administration, isosorbide mononitrate is well absorbed, a haemodynamic effect being measurable within 15-20 minutes. In contrast to isosorbide dinitrate, the mononitrate is not subject to first-pass metabolism.

Dosage and Administration: For oral administration.

Adult dose: Mono-Cedocard 20 — one or two tablets to be taken two or three times daily. Mono-Cedocard 40 — one tablet twice a day taken after meals. The tablets should be swallowed (without chewing) with a little water.

Dosage for the Elderly: The dosage of nitrates in cardiovascular disease is usually determined by patient response and stabilisation. Clinical experience has not necessitated alternative advice for use in elderly patients.

There is no dose recommendation for children.

Contra-indications, Warnings, etc.

Contra-indications: In acute myocardial infarction with low filling pressures. In acute circulatory failure (shock, vascular collapse). When blood pressure is very low. During the first three months of pregnancy.

Warnings/Precautions: Consumption of alcohol should be avoided during treatment, as reaction

Adverse effects: Generally, no serious effects are to be expected. Headache, dizziness, fatigue, palpitations, orthostatic hypotension and flushing may occur, especially at the beginning of treatment. These reactions can usually be controlled by a temporary dosage reduction.

Treatment of overdosage: Gastric lavage, passive exercise of the extremities of the recumbent patient will promote venous return.

Pharmaceutical Precautions:

Storage: Protect from heat and moisture.

Legal Category:

Mono-Cedocard 20: POM

Mono-Cedocard 40: P

Package Quantities:

Mono-Cedocard 20: 100 tablets

Mono-Cedocard 40: 60 tablets

Further Information:

The plasma half-life of isosorbide mononitrate is 4.2 hours.

Product Licence Number

Mono-Cedocard 20: PL 0424/0040

Mono-Cedocard 40: PL 0424/0054

Basic NHS Cost

Mono-Cedocard 20: £8.77 per 100 tablets

Further information available from:



Isolated atrial amyloid contains atrial natriuretic peptide: a report of six cases

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SUMMARY Twenty five specimens of the human right atrial appendage were examined for immunoreactivity to α human atrial natriuretic peptide. In the electron microscope characteristic amyloid fibrils were identified around small blood vessels and adjacent to atrial muscle cells in eight of the surgical cases and in two necropsy cases. In six cases, four surgical and two necropsy, these fibrils contained immunoreactive α human atrial natriuretic peptide. Amyloid is known to occur in peptide secreting endocrine tumours and immunoreactive peptide may be incorporated in the amyloid matrix. The demonstration of atrial amyloid containing immunoreactive α human atrial natriuretic peptide suggests that some deposits of cardiac amyloid are of a type analogous to that found in other endocrine organs.

Amyloidosis is a disorder characterised by the deposition of an abnormal protein usually in the extracellular tissues. It occurs as a primary disease process or secondary to several diverse conditions and the nature of the protein may differ from type to type. Amyloid has characteristic chemical staining reactions and is best defined by its appearance on electron microscopy which shows fine non-branching fibrils approximately 10 nm in diameter. Amyloid deposits occur in endocrine organs and may contain hormone related peptides.¹ For example, immunoreactive calcitonin is found in amyloid deposits associated with medullary carcinoma of the thyroid.^{2,3}

It is now thought that the heart has an important endocrine role in the control of body fluid volume. Small molecular weight peptides have been isolated from the human atria and these have powerful natriuretic and diuretic effects.⁴ Of these, the α human atrial natriuretic factor is believed to be the active circulating form. These peptides have been localised to neurosecretory granules within atrial muscle cells.

During a study of the distribution and staining characteristics of neurosecretory granules in the

human right atrial appendage several cases of amyloid were coincidentally seen. In this report we describe the immunohistochemical localisation of α human natriuretic peptide to amyloid fibrils in the human atrial appendage. This finding suggests that some deposits of cardiac amyloid are of a type analogous to those found in other endocrine organs.

Patients and methods

Twenty two right atrial appendages were obtained at the time of cardiac bypass surgery from patients aged 19-73 years. Three right atrial appendages were obtained at necropsy from patients aged 53 (male), 71 (male), and 88 (female) years. Tissue was removed 24, 48, and 72 hours after death respectively. Two samples of ventricular tissue were also studied, one obtained at necropsy and the other at surgery for ventricular tachycardia.

All of the surgical patients had ischaemic heart disease with or without previous infarction and none was known to have disease processes usually associated with amyloidosis. None had congestive cardiac failure. One patient had an aortic valve replacement in addition to coronary bypass surgery and one patient (a man of 43) had preoperative paroxysmal atrial fibrillation. There were no other reported rhythm disturbances. The patient with ventricular tachycardia had right ventricular dysplasia. Table 1 shows the clinical details and cause of death in the necropsy cases.

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Table 1 Clinical details and cause of death in patients in whom tissue was obtained at necropsy

Age (yr)	Clinical details	Cause of death
53	Hypertension	Cerebrovascular accident
71	Peripheral vascular disease, hypertension	Myocardial infarction
88	Senile dementia, previous cerebrovascular accident	Pulmonary embolism

METHODS

The method of immunohistochemical staining has been reported elsewhere.⁵ In brief, a piece of right atrial appendage was pinned out and fixed in paraformaldehyde lysine sodium periodate for 24 hours. Tissue for routine paraffin histological examination was stained for amyloid by Congo red, sulphated alcian blue, and tryptophan. For immunoelectron microscopy tissue was embedded into an acrylic resin. Ultra thin sections were cut at 50–70 nm, placed on uncoated nickel grids, and stained for atrial natriuretic peptide by indirect immunohistochemical labelling with a 15 nm colloidal gold probe. The rest of the tissue was fixed in glutaraldehyde and osmium tetroxide for standard electron microscopical examination.

The antiserum was also applied to necropsy tissue from the ventricle of a middle aged man with primary cardiac amyloid and to ventricular tissue obtained at surgery that showed no visible amyloid. Control immunocytochemical tests were performed with primary antiserum preabsorbed with synthetic atrial natriuretic peptide or with non-immune rabbit serum.

Results

The age range of the eight patients with amyloid was 43–73 years (mean 60). In eight surgical and two necropsy cases (table 2) ultrastructural examination of the atrial tissue showed fine deposits of amyloid fibrils 7–10 nm in diameter around small blood vessels (arterioles) and adjacent to muscle cells (table 2). None was seen around larger blood vessels. Intracellular amyloid was seen in two cases (fig 1). In four surgical and two necropsy cases the fibrils were clearly and consistently labelled for immunoreactive atrial natriuretic peptide (fig 2). Background labelling of the surrounding connective tissue was negligible. In addition, in all patients immunoreactive atrial natriuretic peptide was demonstrated in the neurosecretory granules within atrial muscle cells (fig 3), which were frequently adjacent to the cell membrane. There was close association between immunoreactive extracellular amyloid deposits and

Kaye, Butler, d'Ardenne, Edmondson, Camm, Slavin

Table 2 Cases of ischaemic heart disease that were positive for amyloid and atrial natriuretic peptide (ANP)

Surgical	Necropsy
22 cases	3 cases
8 positive for amyloid	2 positive for amyloid
4 positive for ANP	2 positive for ANP
4 negative for ANP	

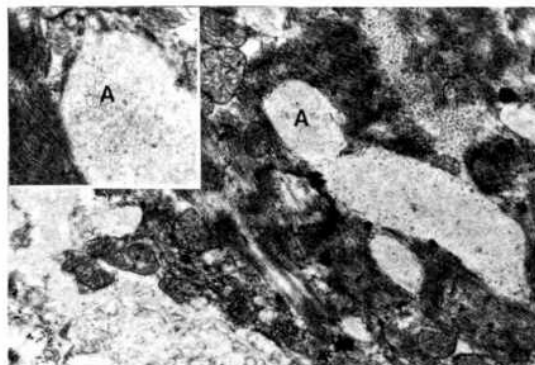


Fig 1 Electronmicrograph showing intracellular amyloid deposits (A) in an atrial muscle cell in atrial appendage tissue fixed in glutaraldehyde and osmium tetroxide.

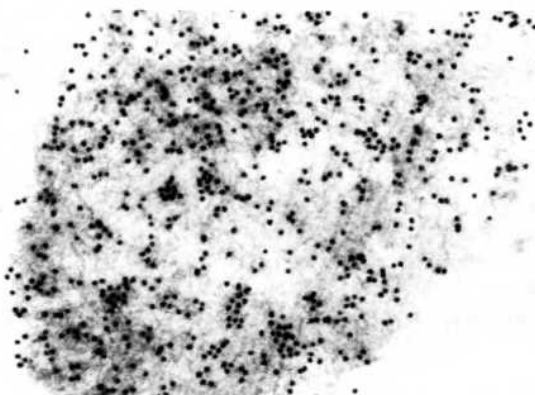


Fig 2 Electronmicrograph showing extracellular amyloid in necropsy tissue from the atrial appendage. Amyloid fibrils are clearly labelled with immunogold (15 nm gold balls) for atrial natriuretic peptide.

neurosecretory granules in amyloid positive patients (fig 4).

In tissue obtained at surgery amyloid was not detected by light microscopy and the Congo red stain was negative. Reaction with preabsorbed anti-atrial natriuretic peptide was consistently negative. In one tissue sample obtained at necropsy from an 88 year old patient, fine deposits of amyloid were

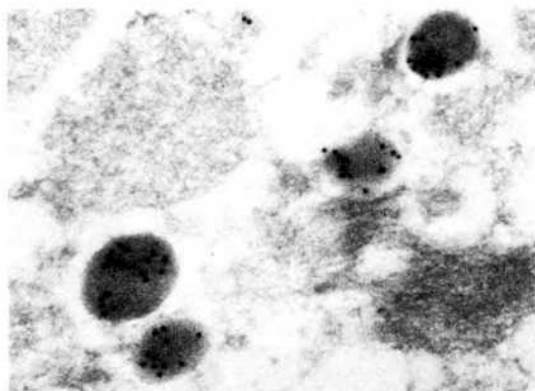


Fig 3 Electronmicrograph showing atrial natriuretic peptide demonstrated by immunogold labelling (15 nm gold balls) in neurosecretory granules in an atrial muscle cell.

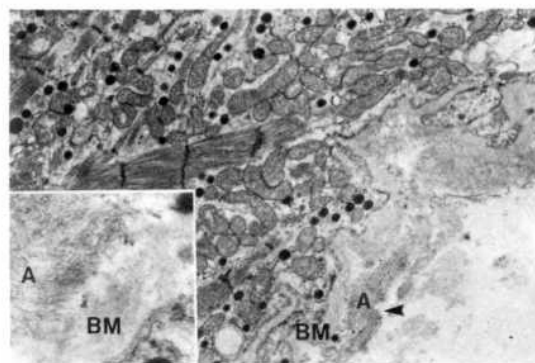


Fig 4 Electronmicrograph showing neurosecretory granules at the periphery of an atrial muscle cell. Amyloid (A) is external to the basement membrane (BM). (Tissue fixed in glutaraldehyde and osmium tetroxide.)

seen by light microscopy. They stained negatively for tryptophan and equivocally for atrial natriuretic peptide.

Neurosecretory granules were not demonstrated in the ventricular tissue examined. A sample from the case of ventricular amyloid, obtained at necropsy, was positive for amyloid by light microscopy. This stained positively for tryptophan but did not react with the antiserum to atrial natriuretic peptide.

The three cases in which tissue was obtained 24, 48, and 72 hours after death were assessed for preservation of immunoreactive atrial natriuretic peptide. All had neurosecretory granules that stained positively for atrial natriuretic peptide. Tissue from the 71 and 88 year old patients, obtained 48 and 72 hours after death respectively, showed isolated atrial amyloid. This stained positively for atrial natriuretic peptide.

Discussion

The aetiology of cardiac amyloid is unknown. Clinical cardiac amyloidosis is a rare disorder in which other organs may or may not be affected. Amyloid deposits sufficient to produce cardiac dysfunction are seldom limited to the heart and are often part of a systemic disorder. Cardiac amyloidosis produces a restrictive type of cardiomyopathy and may present as congestive cardiac failure or with arrhythmias and conduction disturbances that are often associated with sudden death.^{6,7}

More commonly, amyloidosis occurs in a localised form as a manifestation of aging. Two types have been described; that affecting both the ventricles and atria, known as senile cardiac amyloid, and that affecting the atria alone, known as isolated atrial amyloid.⁸ Elderly patients often have small deposits of amyloid in the heart, which rarely cause clinical symptoms although a higher incidence of atrial fibrillation has been noted.⁸ Isolated atrial amyloid has been reported in 78% of patients over the age of 80 years.⁸ Although they are of similar ultrastructural appearance these two forms of cardiac amyloid differ chemically. Senile cardiac amyloid contains easily demonstrable tryptophan, whereas isolated atrial amyloid does not.⁹ In the electron microscope Westermark *et al* observed differences in the type and distribution of cardiac amyloid.¹⁰ They noted that isolated atrial amyloid occurred as fine deposits in or adjacent to the sarcolemma of muscle cells and affected small vessels. Senile cardiac amyloid occurred as larger deposits, often compressing muscle bundles and heavily infiltrating small and medium sized arteries. Only isolated atrial amyloid was found as intracellular deposits.¹⁰ In the present series the distribution and morphological characteristics of the amyloid closely resemble these observations. Intracellular amyloid is also known to occur in endocrine tumours.^{11,12}

Endocrine associated and isolated atrial amyloid are histochemically similar in that, unlike other forms of amyloid, they do not contain tryptophan.^{9,13} We have confirmed the findings for tryptophan staining in patients with senile cardiac amyloid, systemic amyloidosis, and in several tumours containing endocrine amyloid, as well as in isolated atrial amyloid, the latter two conditions being consistently negative for tryptophan.

The discovery of peptides stored within granules in the atria supports the concept that the heart has an endocrine function in the control of body fluids.¹⁴ These peptides have powerful natriuretic, diuretic, and vasodilatory actions⁴ and are believed to be stored as a propeptide molecule within neurosecretory granules. In man the propeptide is

ultimately cleaved into three distinct peptides, α , β , and γ .¹⁵ The α human atrial natriuretic peptide is believed to be the active circulating form and has been measured in the peripheral circulation.¹⁶ It is 28 amino acid residues in length and does not contain tryptophan.

We found immunoreactive α human atrial peptide within atrial amyloid fibrils and demonstrated its presence in the close anatomical association with neurosecretory granules within atrial muscle cells. It is morphologically similar to previous descriptions of isolated atrial amyloid. This supports the concept that some isolated atrial amyloid is of the endocrine associated type and that atrial natriuretic peptide or its precursor may be its primary constituent. In four surgical atrial specimens, however, amyloid did not contain α human atrial natriuretic peptide. There may be several explanations for this. The deposits may represent an early manifestation of generalised cardiac involvement either senile in type or of a clinical secondary type. Alternatively, the negative fibrils may be of an endocrine associated type whose peptides were not recognised by the antiserum. Because ventricular tissue or tissue from other organs was not available in these four cases we are unable to follow this point further.

Previously reported series in which light microscopy was used indicate that both isolated atrial amyloid and senile cardiac amyloid occur with increasing age,^{17,18} usually above the age of 80 years.⁸ In our series the surgical patients were considerably younger. We saw small deposits of amyloid by light microscopy in tissue obtained at necropsy from an 88 year old woman. This patient was in the typical age range for isolated atrial amyloid. It is interesting to speculate that deposits of amyloid may accumulate asymptotically earlier in life than had been appreciated and that this is only revealed by electron microscopy. In the elderly population it has been suggested that atrial fibrillation is more common in patients with isolated atrial amyloid.⁸ It would be difficult to demonstrate levels of cardiac amyloid in younger patients with paroxysmal or sustained atrial fibrillation but the possibility of an association is intriguing.

Cantin *et al* observed immunoreactive atrial natriuretic peptide in neurosecretory granules in atrial tissue obtained within 10 hours of death.¹⁹ However, we have demonstrated immunoreactive atrial natriuretic peptide within neurosecretory granules and amyloid in tissue obtained up to 72 hours after death. This had similar staining characteristics to surgical tissue and this allowed adequate characterisation of atrial natriuretic peptide staining in necropsy tissue. A study is currently under way into the incidence and distribution of atrial amyloid in all age groups and its relation to atrial natriuretic peptides.

Kaye, Butler, d'Ardenne, Edmondson, Camm, Slavin

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Cardiac abnormalities in familial palmoplantar keratosis

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SUMMARY Cardiac abnormalities were identified in patients with familial palmoplantar keratosis. All of them were descended from families on the Greek island of Naxos. Four families were studied and nine cases of palmoplantar keratosis were identified; seven of them showed symptoms and signs of heart disease. Cardiomegaly on chest x ray and electrocardiographic abnormalities were common findings. Three cases had episodes of ventricular tachycardia and a fourth patient died suddenly. All patients with cardiac signs and symptoms showed echocardiographic enlargement of the right ventricle and a right ventricular band; in three the left ventricle was also affected.

Several forms of hereditary palmoplantar keratosis are recognised in Mediterranean countries. In Greece the most common form is Meleda disease.^{1,2}

Because recurrent ventricular tachycardia developed in two young patients with palmoplantar keratosis from the Greek island of Naxos we sought evidence of cardiac abnormalities in families on this island that included members with this dermatosis.

Patients and methods

We identified four families from the Greek island of Naxos that included known cases of palmoplantar keratosis (fig 1). All available family members underwent clinical examination including a detailed history of cardiac events, electrocardiography at rest, and chest radiography. The histories of those who had died were supplied by their families. Patients with palmoplantar keratosis and all other living family members with cardiac abnormalities were examined by echocardiography. We used an Aloka apparatus model SSD 720 and a 3 MHz mechanical transducer to obtain parasternal long and short axis views and apical and subxiphoid two and four chamber views. Right and left ventricular dimensions were measured on M mode echocardiograms obtained during diastole.³ A mean (SD) right to left ventricular diameter ratio of 0.33 (0.06) was regarded as normal.⁴

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Results

PATIENTS WITH PALMOPLANTAR KERATOSIS

We identified nine cases, six male and three female (mean age 24.5 (range 7-41) years), of palmoplantar keratosis (table 1).

Extracardiac anomalies

All patients had pale yellow diffuse palmar and plantar keratoses with clear borders that had appeared between the sixth and twelfth month. They all had dense, rough, dull, and bristly scalp hair resembling steel wire (fig 2). Six patients had short fingers and four of them also had curved nails; their hands or arms were generally rather small.

Cardiac history

Six patients gave a history of paroxysmal tachycardia, palpitation, or syncope (table 1). Three of them (cases 1, 3, and 4) had documented episodes of severe ventricular tachycardia. Patients 1 and 3 who had recurrent ventricular tachycardia that was resistant to medical treatment were initially regarded as cases of Ebstein's anomaly. In patient 1 the diagnosis of Ebstein's anomaly had led to investigation by cardiac catheterisation and replacement of the tricuspid valve. In patient 3 Ebstein's anomaly was excluded by cardiac catheterisation, coronary arteriography, and electrophysiological study at the National Institutes of Health, Bethesda, Maryland. There was evidence of right ventricular enlargement, segmental wall motion abnormalities of both

ventricles, and recurrent drug resistant ventricular tachycardia with left bundle branch block configuration. Biventricular endomyocardial biopsy showed hypertrophy of myocardial cells without fibrosis or cellular infiltration.

Cardiac signs

Four patients had a fourth heart sound and in another two a 2/6–3/6 high pitched midsystolic murmur was heard over the lower left sternal border. In patient 1 the signs were that an atrioventricular prosthesis was functioning normally (table 1).

Electrocardiographic findings

The electrocardiogram was abnormal in all seven patients (table 2). Patients 1 and 5 had right and left abnormal QRS axis deviation respectively. Two patients had right bundle branch block and in the other five the QRS complex was more than 100 ms wide, which is consistent with an intraventricular conduction defect. Moreover, all seven patients had inverted T waves in the precordial leads; in the youngest patient (patient 2) T wave inversion in leads V1 to V3 was regarded as normal. Abnormal Q waves were present in three patients (cases 5, 6, and

Table 1 Clinical data on 9 patients with palmoplantar keratosis

Case No	Age (yr)	Sex	Scalp hair abnormalities	Brachydactyly	Curved nails	Cardiac signs	Cardiac events (age at onset)
1	26	M	+	+	+	AVP	Recurrent VT (17 yr)
2	7	M	+	–	–	Normal	Asymptomatic
3	32	M	+	+	+	S4	Recurrent VT (28 yr)
4	17	M	+	–	–	S4	VT × 2 (17 yr)
5	26	M	+	+	–	S4	Syncope × 3 (21 yr)
6	19	M	+	–	–	SM	Asymptomatic
7	17	F	+	+	+	SM	Syncope × 1 (16 yr)*
8	41	F	+	+	–	S4	Palpitation (31 yr)
9	36	F	+	+	+	Normal	Asymptomatic

AVP, atrioventricular prosthesis; S4, fourth heart sound; SM, systolic murmur; VT, ventricular tachycardia.

*The patient died suddenly a few months later.

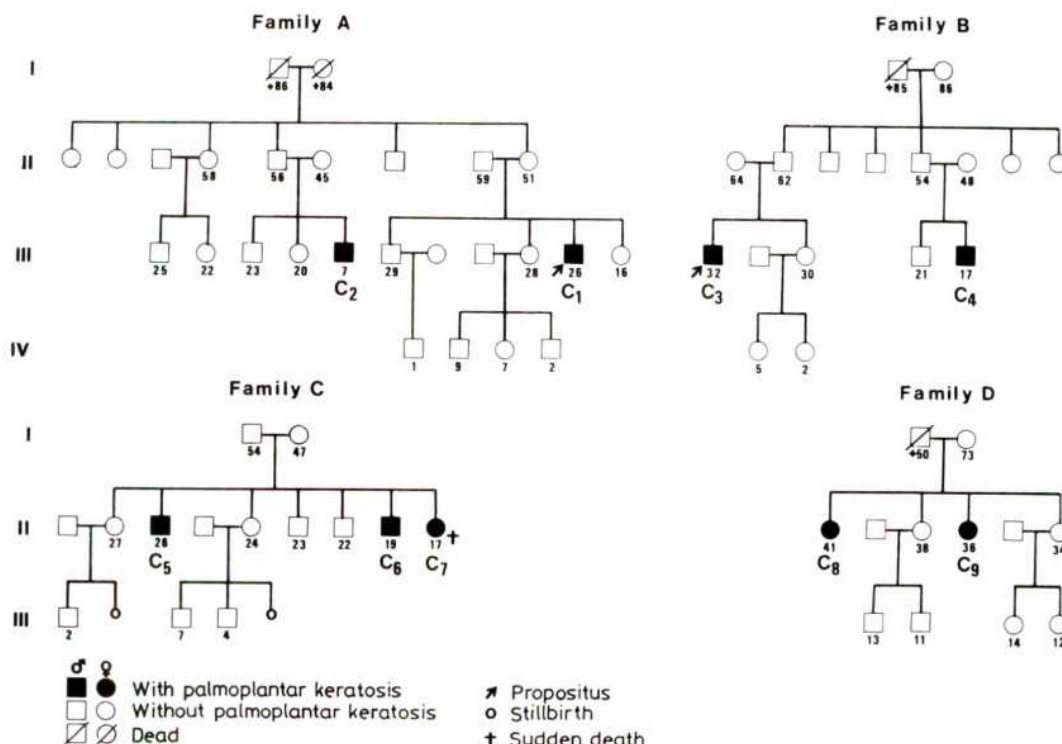


Fig 1 Pedigrees of four families from the Greek island of Naxos. Case (C) numbers refer to patients with palmoplantar keratosis in text and in table 1. Individual ages in 1985, or age at time of death are given.

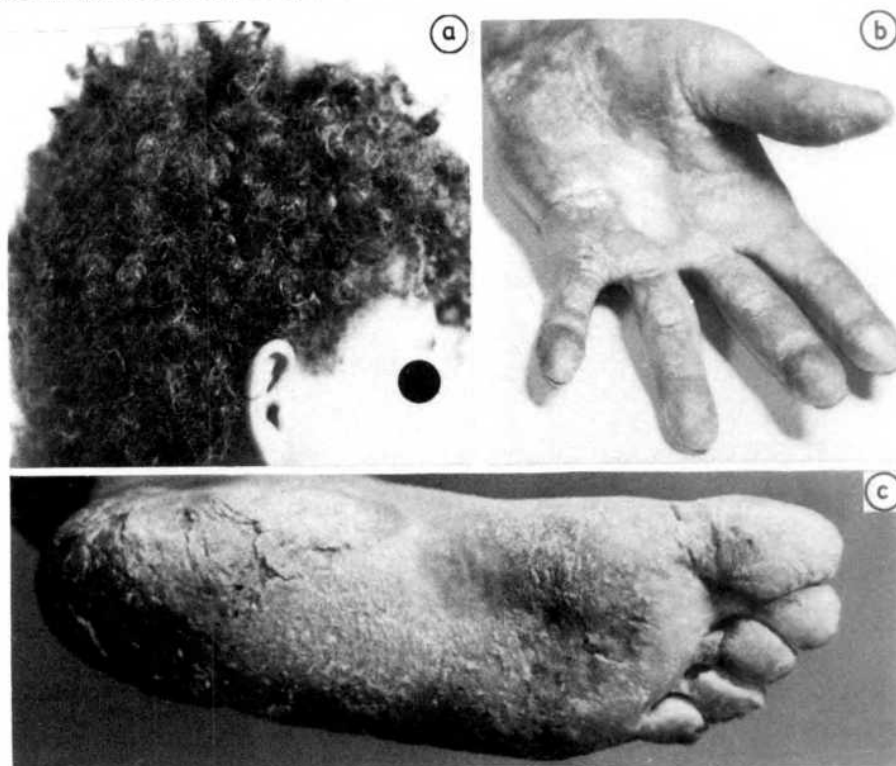


Fig 2 Hair, palms, and soles in palmoplantar keratosis. (a) The scalp hair was dense, rough, and bristly. (b) Keratosis of the palmar folds and the medial sides of the fingers. (c) Keratosis uniformly covering the soles of the feet.

8). Patients 1, 7, and 8 had low voltage electrocardiograms (R wave <0.5 mV in limb leads and 1 mV in the precordial leads).

Arrhythmias

All patients were in normal sinus rhythm, except patient 1 who had atrial fibrillation. In six patients there were frequent extrasystoles, mainly of right ventricular origin. In patient 8, who complained of

palpitation, no ventricular extrasystoles were recorded at rest. Episodes of ventricular tachycardia of left bundle branch block configuration (fig 3) were recorded in three cases (table 3); a fourth patient (case 7) with ventricular extrasystoles died suddenly.

Chest radiography

The heart size was increased (cardiothoracic ratio >0.50) in seven cases (table 2). In patient 1 the

Table 2 Electrocardiographic, radiographic, and echocardiographic findings in 9 patients with palmoplantar keratosis

Case No	Cardiac rhythm	QRST electrocardiogram				X ray CT ratio	Echocardiography		
		QRS axis	QRS width (ms)	QRS configuration	Inverted T waves		RVEDD (mm)	LVEDD (mm)	RV:LV ratio
1	AF, ES, VT	+135	140	IVCD	V1-V6	0.68	80	37	2.16
2	NSR	+90	80	Normal	V1-V3	0.50	12	32	0.37
3	NSR, ES, VT	-30	120	IVCD	V1-V4	0.56	34	43	0.79
4	NSR, ES, VT	-30	160	RBBB	V1-V4	0.52	32	42	0.76
5	NSR, ES	-75	120	IVCD	V1-V6	0.64	42	63	0.67
6	NSR, ES	+100	140	RBBB	V1-V6	0.51	43	48	0.90
7	NSR, ES	-30	120	IVCD	V1-V6	0.61	40	60	0.67
8	NSR	-30	120	IVCD	V1-V4	0.56	36	51	0.70
9	NSR	+60	100	Normal	—	0.42	11	40	0.28

AF, atrial fibrillation; CT, cardiothoracic; IVCD, interventricular conduction defect; LV, left ventricle; LVEDD, left ventricular end diastolic diameter; NSR, normal sinus rhythm; ES, extrasystole; RBBB, right bundle branch block; RV, right ventricle; RVEDD, right ventricular end diastolic diameter; VT, ventricular tachycardia.

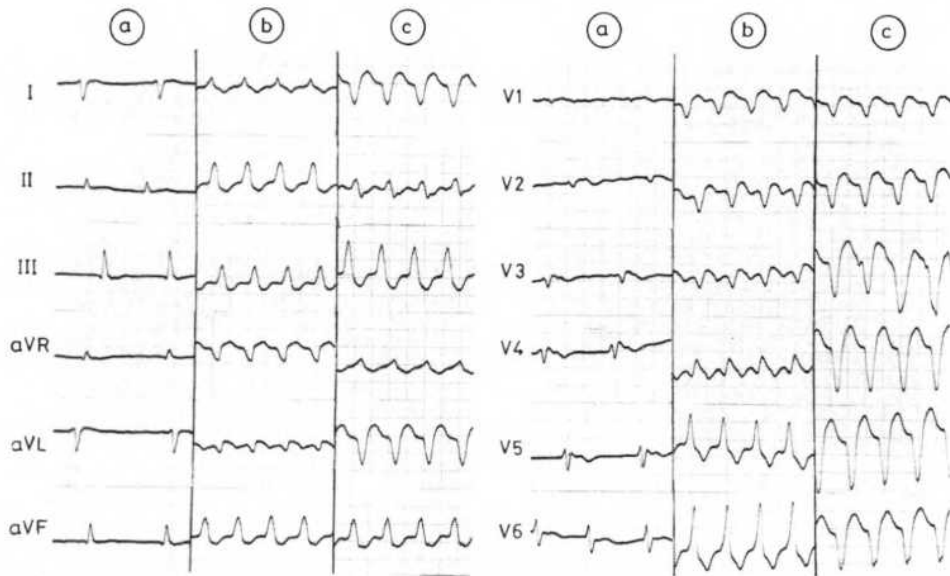


Fig 3 Normal electrocardiogram (a) and two episodes of ventricular tachycardia (b and c) in patient 1 (single channel recorder). In (a) there was a QRS axis of >135 ms, QRS prolongation, low voltage, and T wave inversion in the precordial leads. In both (b) and (c) the ventricular tachycardia rate is 160 beats per minute and the QRS axes were >75 ms and >135 ms respectively.

cardiac silhouette was oversized, with gross right atrial and right ventricular dilatation. Pulmonary vasculature was normal.

Echocardiography

In seven of the nine patients the right ventricular end diastolic diameter was enlarged and the ratio of the diameters of right and left ventricles was increased

(range 0.67–2.16) (table 2). Two of them (cases 5 and 7) also had left ventricular dilatation with diffuse hypokinesia of both ventricles. There was moderate hypokinesia of the left ventricle in patient 8 in whom the left ventricular end diastolic diameter was in the upper limit of normal. In patient 1, who had severe right ventricular hypokinesia, the right ventricle and right atrium were grossly enlarged. The inter-

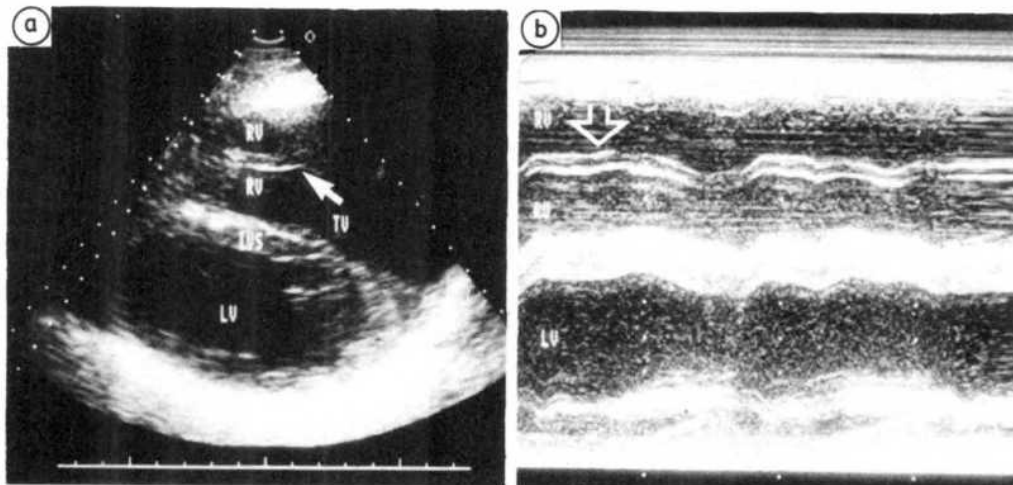


Fig 4 Cross sectional (a) and M mode (b) images of patient 4 in the modified long axis parasternal view. An echodense muscular type band (arrows) parallel to the interventricular septum (IVS) is present in the right ventricle (RV). LV, left ventricle; TV, tricuspid valve.

Table 3 Documented episodes of VT in three of our patients

Case No	Age (yr) at episode	Symptoms	Electrocardiogram during VT			
			QRS axis (ms)	QRS configuration	Rate (beats per min)	Termination of VT
1	25	Palpitation, collapse	+75	LBBB	160	DC shock
	25	Palpitation, dizziness	+135	LBBB	160	DC shock
	26	Palpitation, dizziness	+135	LBBB	150	DC shock
3	28	Palpitation, syncope	+75	LBBB	260	DC shock
	28	Palpitation, dizziness	+75	LBBB	210	DC shock
	29	Palpitation, dizziness	+120	LBBB	150	DC shock
4	17	Palpitation, syncope	+75	LBBB	210	Lignocaine
	17	Palpitation, dizziness	+75	LBBB	140	Lignocaine

LBBB, left bundle branch block; VT, ventricular tachycardia.

ventricular septum moved paradoxically in two patients (cases 1 and 5) and was hypokinetic in another two (cases 7 and 8). Neither right nor left ventricular hypertrophy was seen. In all the cases with an enlarged right ventricle there was an echodense muscular band that originated from the right apex and ran parallel to the interventricular septum (fig 4). Mitral valve prolapse was found in one patient (case 2).

FAMILY MEMBERS WITHOUT PALMOPLANTAR KERATOSIS

We were able to examine 40 members of the study families who did not have palmoplantar keratosis (fig 1). Except for a case of mitral valve prolapse none had cardiac abnormalities. None of these who had died was reported to have died suddenly or to have had skin lesions or heart disease.

Discussion

PALMOPLANTAR KERATOSIS

Palmoplantar keratosis is a familial ectodermal defect characterised by hyperkeratosis of the palms and soles.⁵ It is occasionally seen in association with brachydactyly or nail anomalies.² Meleda disease typically affects not only the palms and soles but also the backs of the hands and feet and is often associated with short cone shaped fingers and nail abnormalities (koilonychia, pachyonychia) but not scalp hair abnormalities.^{2,6} The only palmoplantar keratosis with scalp hair anomalies (similar to the ones noted in our cases) is leuconychia totalis.⁷ Palmoplantar keratosis has been reported to occur in association with dental lesions, deafness, ophthalmic anomalies, and oligophrenia,^{2,6,7} but not cardiac abnormalities. Our pedigree studies suggested that this is an autosomal recessive trait (fig 1). All four families came from the island of Naxos but many members were born and are living in several parts of Greece.

CARDIAC DISORDERS

The occurrence of strikingly similar cardiac abnor-

malities in most of our patients with palmoplantar keratosis cannot be regarded as a coincidence. The common cardiac disorder shared by our patients were electrocardiographic abnormalities, cardiomegaly, and echocardiographic evidence of predominantly right ventricular abnormalities. The electrocardiographic disorders noted in our patients included intraventricular conduction delays, T wave inversion in the precordial leads, abnormal Q waves, low voltage, and also arrhythmias of ventricular origin (ventricular extrasystoles, recurrent ventricular tachycardia with left bundle branch block configuration). The echocardiographic abnormalities consisted of cardiac enlargement mainly of the right ventricle, wall motion abnormalities, and an echodense muscular type band originating from the right apex.

Possible differential diagnoses of heart disease in our patients are dilated cardiomyopathy and arrhythmogenic right ventricular dysplasia.

The age and sex of our patients and the electrocardiographic disorders, right ventricular enlargement, and recurrent episodes of ventricular tachycardia accord with the features of dilated cardiomyopathy predominantly affecting the right ventricle.^{8,9} But there was no clinical evidence of heart failure in any of our patients. Similarly, paradoxical interventricular septal motion was found in only two of our patients but it was a common echocardiographic feature in all cases of dilated cardiomyopathy of the right ventricle described by Fitchett *et al.*⁹ Also the prominent right ventricular band found in several of our patients is uncommon in dilated cardiomyopathy. Paraseptal structures were seen in the right ventricle of most patients with dilated cardiomyopathy who were candidates for cardiac transplantation.¹⁰ A biventricular endomyocardial biopsy performed on patient 3 showed no evidence of active inflammation or fibrosis. Necropsy was not performed on patient 7 who died suddenly on the island of Naxos.

The syndrome of arrhythmogenic right ventricu-

lar dysplasia consists of isolated right ventricular myopathy and recurrent ventricular tachycardia.^{4 11 12} Three of our patients (cases 1, 3, and 4) developed the principal features of this syndrome. They were young men who presented with recurrent ventricular tachycardia of left bundle branch block configuration. The resting electrocardiograms showed T wave inversion in the anterior precordial leads and differing degrees of delayed right ventricular activation. Ventricular post-excitation waves were seen in V1 and V2 on the electrocardiogram of patient 4 despite the recording being at normal sensitivity. Echocardiography showed isolated dilatation of the right ventricle with an increase in the ratio of right to left ventricular diameters. Right ventricular enlargement was also seen in the other four patients with cardiac signs and symptoms. Three of these had left ventricular dysfunction at rest. Although the left ventricular dysfunction accompanying arrhythmogenic right ventricular dysplasia was easily uncovered by exercise,¹³ its presence at rest was reported with variable frequency.^{4 12}

The familial occurrence of right ventricular dilated cardiomyopathy¹⁴ and arrhythmogenic right ventricular dysplasia has been reported.¹⁵ In each report only one family was identified and the patients were siblings of the same family.

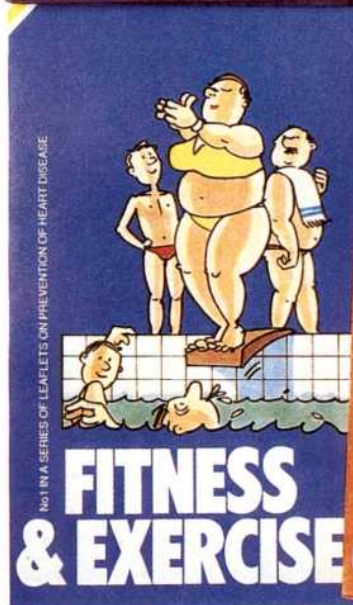
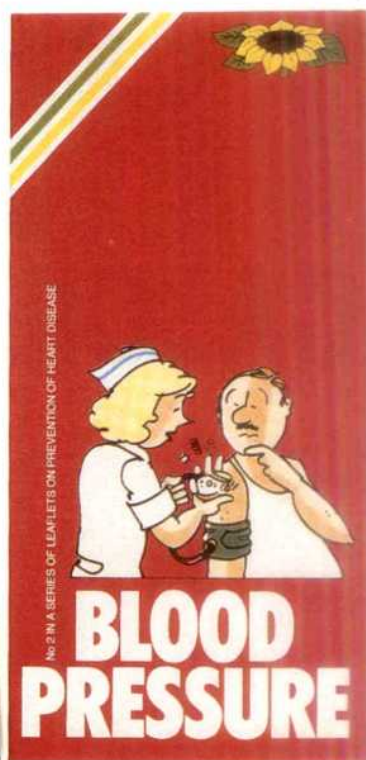
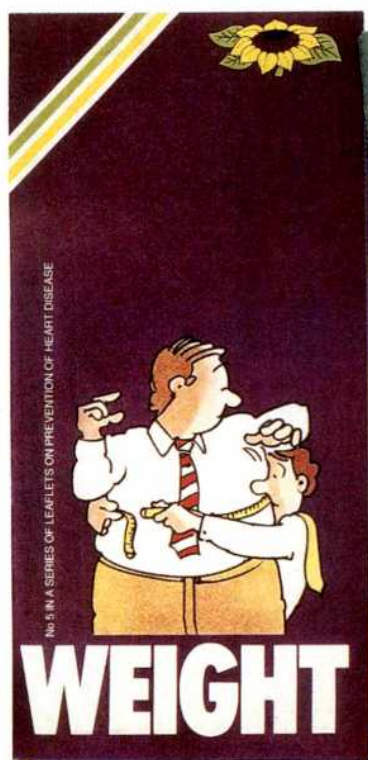
Patient 1 may have had Ebstein's anomaly with additional myocardial dysplasia, as shown by the huge right ventricle, the prominent right ventricular band, and recurrent ventricular tachycardia.^{16 17}

We believe that our cases have a familial or possibly an autosomal recessive hereditary disorder that is characterised by both palmoplantar keratosis and right ventricular dysplasia causing potentially lethal arrhythmias. Further studies are in progress.

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Left ventricular dysfunction in patients with angina pectoris and normal coronary angiograms

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From the Regional Cardiac Centre, Wythenshawe Hospital, Manchester

SUMMARY Left ventricular function was assessed in 201 patients who presented with angina pectoris and who were subsequently found to have completely normal coronary angiograms. Left ventricular angiograms from 187 patients were suitable for analysis of systolic regional wall motion; 121 were found to be normal and 66 had a total of 115 hypokinetic segments. Patients with hypokinesia had a significantly higher left ventricular end systolic volume and a significantly lower left ventricular ejection fraction and exercise capacity than those in whom regional wall motion was normal. Thirty one per cent of patients with normal wall motion and 30% of those with hypokinesia had a resting left ventricular end diastolic pressure > 15 mm Hg. There were significantly more smokers in the group with hypokinetic segments.

Thus of patients with angina and normal coronary angiograms, 25% had evidence of left ventricular systolic dysfunction, 20% had evidence of diastolic dysfunction, and 11% had evidence of both systolic and diastolic dysfunction. The results suggest that smoking may be associated with left ventricular regional wall motion abnormalities.

The occurrence of angina pectoris despite normal coronary angiograms is a common clinical problem^{1,2} that is frustrating for both the patient and physician. Some investigators have suggested that in many of these patients the cause of the pain is non-cardiac. Oesophageal^{3,4} and psychosomatic⁵ causes have been suggested. Others, however, have shown that many of these patients have abnormal exercise electrocardiograms,^{6,7} abnormal lactate metabolism during infusion of isoprenaline or atrial pacing,^{8,9} and reduced coronary vasodilator reserve.¹⁰ Richardson *et al* in 1974 reported seven patients with angina and normal coronary angiograms in whom endomyocardial biopsy specimens showed features of congestive cardiomyopathy.¹¹ More recently radionuclide angiography has been used to show that some patients with chest pain and normal coronary arteries have left ventricular dysfunction during exercise.^{12,13}

We have studied a large group of patients presenting with typical angina pectoris who had

completely normal coronary angiograms. The study was designed to assess systolic and diastolic left ventricular function and to relate these variables to clinical features and the results of non-invasive investigations.

Patients and methods

PATIENT POPULATION

Two hundred and one patients (99 men and 102 women aged 27-64 (mean 45.4) years) with angina pectoris were found to have normal coronary angiograms when they were studied at the regional cardiac unit between July 1981 and June 1984. Unlike many previous studies, we did not include patients with even minor irregularities on the coronary arteriogram. We also excluded patients with variant angina, atypical chest pain, hypertrophic obstructive cardiomyopathy, uncontrolled hypertension, important valvar heart disease, or clinical or radiological evidence of cardiac failure.

HISTORY AND EXAMINATION

The history was taken independently by at least two members of the cardiac unit. The presence or absence of five features of chest pain was noted: site

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(retrosternal, with and without left chest pain), character (constricting, gripping, pressing), radiation (left arm, shoulder, neck, jaw), usual precipitating factors (exercise, emotion, cold weather), and usual relieving factors (relief within 10 minutes of resting or taking glyceryl trinitrate).

The presence or absence of five risk factors was also noted. Patients were classified as smokers if they had smoked at least 40 cigarettes per week for at least 10 years.¹⁴ A diastolic blood pressure that had been consistently > 100 mm Hg was regarded as evidence of systemic hypertension, although only patients who became normotensive on treatment were included in the study. The presence of diabetes mellitus (treated with diet, oral hypoglycaemics, or insulin) and a family history of ischaemic heart disease¹⁴ (angina or myocardial infarction in parents, grandparents, or siblings) were determined. Patients were regarded as being overweight if they were at least 15% above the mean weight for their height and sex.¹⁵

ELECTROCARDIOGRAPHY AND EXERCISE TESTING

A standard 12 lead electrocardiogram was obtained in all 201 patients, none of whom were being treated with digoxin. Symptom limited treadmill exercise testing was performed according to a standard Bruce protocol. The development of chest pain during exercise, and exercise capacity as percentage of the predicted normal value for their age and sex¹⁶ were noted. ST segment depression (≥ 1 mm from resting values for horizontal or downsloping depression or ≥ 2 mm for upsloping depression) that developed 0.08 s after the J point was regarded as abnormal.¹⁷

CARDIAC CATHETERISATION

Selective coronary angiography was performed in multiple views in all patients. Resting left ventricular end diastolic pressure was measured before

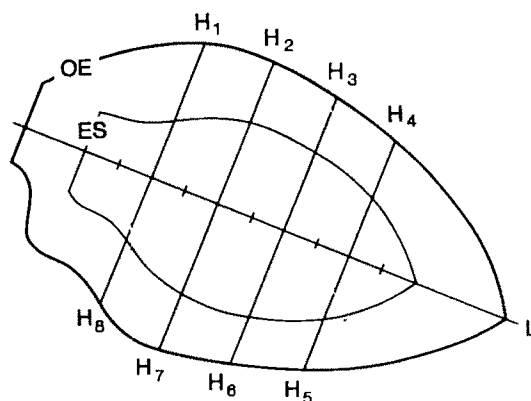


Fig 1 Ventricular silhouettes at onset of ejection (OE) and at end systole (ES). The hemaxes (H_1 - H_8) divide the end systolic longitudinal axis (L) into five equal lengths.

angiography in a standard manner with a Hewlett-Packard quartz transducer (1290C) and a Hewlett-Packard photographic recorder (8890B). A left ventricular angiogram was obtained in the right anterior oblique projection in all subjects. We noted which patients had been receiving treatment with a β blocker or a calcium antagonist or both before cardiac catheterisation.

The coronary angiograms, which were reviewed by at least three experienced observers, were all confirmed to be normal. The left ventricular angiograms included in this study were ones in which the left ventricular walls were clearly outlined by contrast material so that silhouettes could be traced. The cycles analysed were sinus beats that did not follow extrasystoles. Left ventricular angiograms suitable for analysis were obtained from 187 patients; left ventricular end systolic and end diastolic volumes and ejection fractions were calculated by means of the single plane area-length

Table 1 Clinical characteristics of groups 1 and 2 and the control group

	Group 1 (n = 121)	Group 2 (n = 66)	Control (n = 20)
Age (years) (mean (SD))	46.0 (7.8)	44.0 (9.3)	54.0 (11.5)†
Sex			
Male	58 (48%)	37 (56%)	6 (30%)
Female	63 (52%)	29 (44%)	14 (70%)
Characteristics of chest pain (mean (SD))*	3.80 (0.88)	4.08 (0.75)†	
Number treated with β blocker	75 (62%)	44 (67%)	0 (0%)‡
Number treated with calcium antagonist	65 (54%)	37 (56%)	0 (0%)‡
Number treated with both β blocker and calcium antagonist	48 (40%)	28 (42%)	0 (0%)‡

*Presence of characteristic features of chest pain (Score 0-5.)

†Significantly different from group 1, $p < 0.05$.

‡Significantly different from groups 1 and 2, $p < 0.01$.

Group 1, patients with no hypokinetic segments.

Group 2, patients with hypokinetic segments.

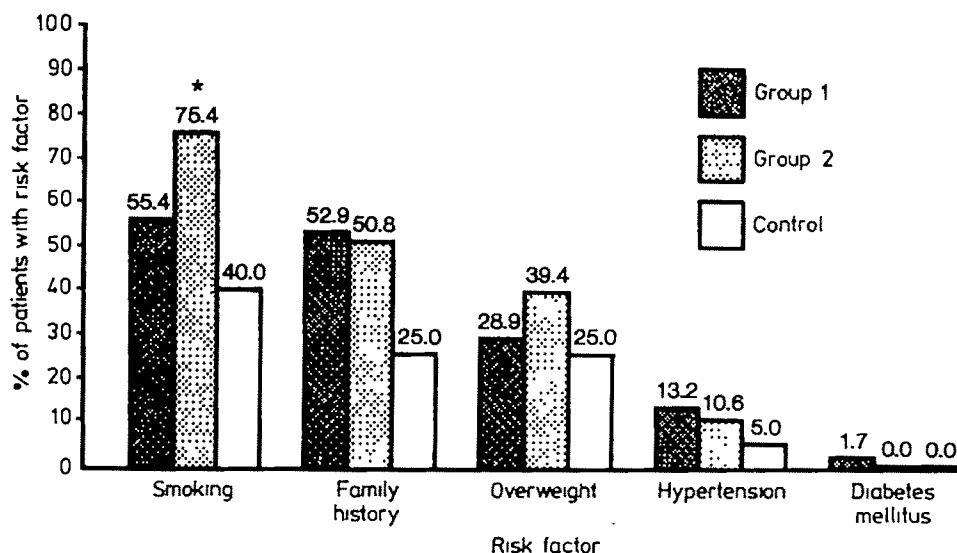


Fig 2 Frequency of five coronary risk factors in patients with no hypokinetic segments (group 1) and patients with hypokinetic segments (group 2) and the control group. *Significantly different from group 1 and the control group, $p < 0.01$

method after correction for magnification.¹⁸ Left ventricular regional wall motion was measured by the technique described by Leighton *et al.*¹⁹ The outlines of the ventricle at the onset of ejection and at end systole were traced from the projected ventriculogram. A longitudinal axis of the ventricular silhouette on the onset of ejection frame was drawn through the apex so that it divided the ventricle into two equal areas. After correction for rotation, four lines were drawn perpendicularly to the longitudinal axis, dividing the end systolic axis into five equal segments. The percentage of systolic motion in seven hemiaxes (H_1 – H_7 , fig 1) was calculated and compared with reported normal values.¹⁹ Regions in which the percentage of systolic motion was < 2 SD from the normal mean were defined as being hypokinetic. One hemiaxis (H_8 , fig 1) did not prove useful in defining regional wall motion because of the extreme normal variability in shortening at this site.

A control group was made up of 20 patients who had been investigated because of systolic heart murmurs. None complained of chest pain, all had normal coronary angiograms but they did have trivial aortic valve disease (aortic valve systolic gradient < 20 mm Hg).

We examined the group differences by a one way analysis of variance and compared proportions by the χ^2 test.

Results

Of the 187 patients who had left ventricular angiograms that were suitable for analysis, 121 had no hypokinetic segments (group 1) and 66 had a total of 115 hypokinetic segments (group 2); 39 had one hypokinetic segment, 11 had two, 11 had three, four had four, and one patient had five. Of the 115 hypokinetic segments, 69 occurred on the anterolateral wall (H_1 – H_4) and 46 on the inferior wall (H_5 – H_7). Only one of the 20 controls had a hypokinetic segment.

There was no significant difference in age or sex between groups 1 and 2, but their mean age was significantly lower than that of the controls (table 1). In group 2 chest pain was associated with significantly more of the characteristic features than in group 1 ($p = 0.03$), although chest pain in group 1 was typified by most of the characteristics assessed (table 1). The proportions of patients receiving treatment with a β blocker, a calcium antagonist, or a combination of a β blocker and a calcium antagonist were not significantly different in groups 1 and 2 (table 1). The dosages of β blocker or calcium antagonist administered to the two groups were similar. The mean (SD) dose of atenolol in group 1 (51 patients) was 94 mg (24) mg daily and in group 2 (26 patients) it was 85 mg (27) mg daily. The dose of propranolol was 149 mg (55) mg daily and 160 mg

Table 2 Resting electrocardiogram of patients in groups 1 and 2 and the control group

	Group 1 (n = 121)	Group 2 (n = 66)	Control (n = 20)
Normal	83	46	16
Abnormal:	38	20	4
T wave abnormality*	21	11	3
ST abnormality*	6	4	0
RBBB	8	3	0
LBBB	3	2	1

Group 1, patients with no hypokinetic segments.

Group 2, patients with hypokinetic segments.

RBBB, right bundle branch block; LBBB, left bundle branch block.

*T wave abnormality/ST abnormality.³⁵

(59) mg daily in groups 1 (15 patients) and 2 (13 patients) respectively. Five patients in group 1 were taking oxprenolol (mean 152 mg daily) and two in group 2 (120 mg daily); three patients in group 1 were taking metoprolol (200 mg daily) and two in group 2 (200 mg daily); and one patient in group 1 was taking sotalol (320 mg daily) and one in group 2 (320 mg daily). In group 1 (45 patients) the daily dose of nifedipine was 41 mg (14) mg and in group 2 (24 patients) it was 38 mg (14) mg. Doses of verapamil were 252 mg (86) mg daily (20 patients) and 268 mg (72) mg (13 patients) respectively.

Figure 2 shows the details of the presence or absence of the five coronary risk factors investigated in groups 1 and 2 and the control group. There were significantly more smokers in group 2 than in group 1 and the control group ($p < 0.01$). There was no significant difference, however, in the frequency of the other four risk factors. The total number of risk factors (mean (SD)) per patient, up to a maximum of five, was not significantly different in group 1 (1.5 (0.9)) and group 2 (1.7 (0.9)), but it was significantly greater in both groups 1 and 2 than in the controls (1.0 (0.8), $p < 0.02$).

The resting electrocardiogram was abnormal in 31% of patients in group 1, 30% of patients in group 2, and 20% of the control group (table 2). The commonest abnormality in each group was T wave change, and there was no significant difference in the

Table 3 Results of symptom limited exercise testing in groups 1 and 2

	Group 1 (n = 82)	Group 2 (n = 44)
ST segment response		
Normal	33	23
Abnormal	49	21
Usual chest pain during test:		
Yes	34	26
No	48	18
*Exercise duration as % predicted (mean (SD))	82.5% (32.2)	63.5% (31.1)†

Group 1, patients with no hypokinetic segments

Group 2, patients with hypokinetic segments.

*Percentage of predicted normal value for age and sex.¹⁶†Significantly different from group 1, $p < 0.01$.

resting electrocardiogram between the three groups. Table 3 shows the results of symptom limited exercise testing in 82 patients from group 1 and 44 patients from group 2. There was no significant difference between groups 1 and 2 in the proportion of patients who had abnormal ST segment response to exercise (60% and 48% respectively). Although 59% of patients from group 2 developed their usual chest pain on the treadmill compared with only 41% from group 1, the difference did not reach statistical significance ($p = 0.08$). Exercise duration as a percentage of the predicted normal value was significantly higher ($p < 0.01$) in group 1 (82.5 (32.2)%) than in group 2 (63.5 (31.1)%), indicating that patients with hypokinetic segments had a worse exercise capacity.

Table 4 shows left ventricular volumes and ejection fraction for groups 1 and 2 and the control group. There was no difference in end diastolic volume between the three groups. End systolic volume was significantly higher ($p < 0.01$) and ejection fraction significantly lower ($p < 0.001$) in group 2 than in group 1 and the control group. There was no difference in resting left ventricular end diastolic pressure between group 1 (14.2 (5.1) mm Hg) and group 2 (14.5 (4.7) mm Hg), but in both groups it was significantly higher ($p < 0.001$) than in the control group (10.3 (3.4) mm Hg) (fig 3). Left ventricu-

Table 4 Left ventricular volumes and ejection fraction (mean (SD)) in groups 1 and 2 and the control group

	Group 1 (n = 121)	Group 2 (n = 66)	Control (n = 20)
EDV (ml/m ²)	122.4 (25.2)	126.2 (27.2)	130.7 (19.4)
ESV (ml/m ²)	53.4 (13.9)	68.6 (17.1)*	54.9 (11.2)
EF (%)	56.4 (6.7)	45.8 (5.8)†	57.8 (6.8)

Group 1, patients with no hypokinetic segments.

Group 2, patients with hypokinetic segments.

EDV, left ventricular end diastolic volume; ESV, left ventricular end systolic volume; EF, left ventricular ejection fraction

*Significantly different from group 1 and control group, $p < 0.01$.†Significantly different from group 1 and control group, $p < 0.001$.

lar end diastolic pressure was >15 mmHg in 38 patients (31%) from group 1 and in 20 patients (30%) from group 2 but in none of the control group.

Discussion

There has been much debate as to whether patients with angina and normal coronary angiograms experience true myocardial ischaemia. Various theories have been proposed to explain myocardial ischaemia in the absence of coronary occlusive disease. Disease of the small coronary vessels has been suggested,²⁰ but histological changes in such vessels have never been found by pathologists in the absence of general vascular disorders. Eliot and Bratt suggested the presence of abnormal haemoglobin-oxygen dissociation characteristics,²¹ but this has not been confirmed by other workers. Richardson *et al* suggested the possibility of cardiomyopathy on the basis of myocardial biopsy in a small series of cases,¹¹ and Boden *et al* the possibility that hyperdynamic ventricular contraction increases myocardial oxygen consumption.²² More recently it has been shown that some patients with angina and

normal coronary angiograms have decreased coronary vasodilator reserve.¹⁰

Left ventriculography has not previously been the subject of detailed investigation in a large group of patients with angina and normal coronary angiograms. Objective and subjective analysis of left ventricular angiograms has been examined,²³ and it was found that reproducibility and accuracy required objective analysis. The use of a quantitative method is essential for the proper interpretation of left ventricular wall motion, and the technique that we used also corrects for descent of the aortic valve and rotation of the apex.¹⁹

We found that 35% of patients presenting with angina pectoris who were later found to have normal coronary angiograms had evidence of left ventricular regional wall motion abnormalities. The hypokinetic segments that occurred in these patients were not confined to any particular part of the ventricle. These patients did not have an increased left ventricular end diastolic volume, but they did have a significantly higher left ventricular end systolic volume and a significantly lower left ventricular ejection fraction than patients with normal regional wall motion. Berger *et al* found left ventricular dysfunction during exercise in 12 (39%) of 31 patients with chest pain, normal coronary arteries, and normal resting left ventricular performance.¹²

In our series there was no difference in resting left ventricular end diastolic pressure between patients with hypokinetic segments and those with normal regional wall motion, but in both groups it was significantly higher than in the control group of patients. A resting left ventricular end diastolic pressure >15 mmHg was found in 31% of patients with normal wall motion and 30% of patients with evidence of hypokinesia. Bush *et al* found that of 125 patients with angina, normal coronary angiograms, and normal left ventricular ejection fraction, 75 (60%) had a resting left ventricular end diastolic pressure >12 mmHg or a post-angiographic pressure >22 mmHg or both.²⁴ Some of these patients developed chest pain during cardiac catheterisation; this was always associated with a rise in left ventricular end diastolic pressure to >24 mmHg; glyceryl trinitrate consistently produced relief of pain and a fall in pressure to <12 mmHg. They concluded that these patients had isolated left ventricular diastolic dysfunction. Our results showed that of 187 patients presenting with angina who were found to have normal coronary angiograms, 46 (24.6%) had left ventricular systolic dysfunction at rest, 38 (20.3%) had diastolic dysfunction, and 20 (10.7%) had both systolic and diastolic dysfunction.

We found no difference in the resting electrocardiogram or the ST segment response to exercise

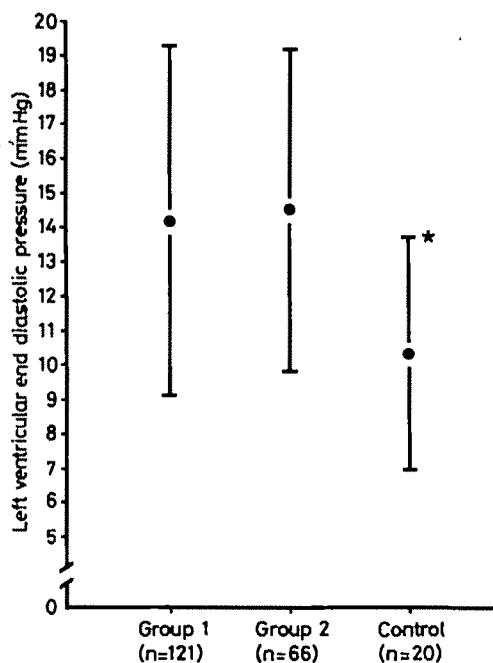


Fig 3 Left ventricular end diastolic pressure in patients with no hypokinetic segments (group 1) and patients with hypokinetic segments (group 2) and the control group.

*Significantly different from groups 1 and 2, $p < 0.001$.

between those patients who had hypokinetic left ventricular segments and those with normal regional wall motion. Exercise capacity as a percentage of the predicted normal value was, however, significantly lower for patients with hypokinetic segments, and these patients were also more likely to develop their usual chest pain during treadmill exercise testing.

Since the work of Richardson *et al.*,¹¹ there have been further reports on the findings of right and left ventricular endomyocardial biopsy in small numbers of patients with angina and normal coronary angiograms.²⁵⁻²⁷ Histological abnormalities have been reported in 48-100% of cases. Patients with congestive cardiomyopathy often complain of chest pain, despite the presence of normal or even large coronary arteries, and they have been found to have reduced coronary blood flow at rest and during cardiac pacing.²⁸ No patient in our series had clinical or radiological evidence of cardiac failure. The cause of left ventricular dysfunction in some patients in this study remains uncertain, but there was a higher incidence of smoking in those with regional wall motion abnormalities. Hartz *et al.* have suggested that smoking is associated with a cardiomyopathy and that the relation is separate from the association of smoking with coronary artery disease.²⁹

Although the prognosis of patients with chest pain and normal coronary arteries has been believed to be benign,^{2,30-34} many previous studies have excluded patients with abnormal left ventricular angiograms^{2,30,31} and have included patients with atypical chest pain.³¹⁻³³ Our findings of mild left ventricular dysfunction in a considerable proportion of patients with typical angina pectoris and normal coronary angiograms raise the possibility that the prognosis in terms of persistence of symptoms and mortality in these patients with left ventricular abnormality may not prove to be as good as has been previously suggested, although currently we do not have any evidence for this.

We thank Dr C L Bray and Dr C Ward for allowing us to study patients under their care. The work described is part of a study submitted by PMS to the University of Manchester for the degree of doctor of medicine.

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Assessment of regional left ventricular function by magnetic resonance

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SUMMARY The ability of magnetic resonance to determine regional left ventricular function was investigated in 18 patients—13 with coronary artery disease (nine with previous infarction), one with congestive cardiomyopathy, one with mitral stenosis, one with an atrial septal defect, and two without detectable cardiac abnormality. Coronal magnetic resonance images were acquired through the aortic valve and sagittal images were acquired in the plane of widest diameter of the left ventricle seen in the coronal image, both at end diastole and end systole. Regional wall motion assessed by magnetic resonance was compared with the results of anteroposterior and left lateral x ray ventriculograms by two independent observers. The left ventricular wall was divided into three segments in each plane and the motion of the segments was classified as normal, hypokinetic, akinetic, or dyskinetic. Muscle thickness was measured in each segment of the magnetic resonance images and was considered to be abnormal if in the systolic images it was <75% of that in neighbouring segments or if it failed to increase by at least 25% between diastole and systole. Wall motion assessments by the two methods agreed in 68 of 105 segments analysed, but differed by one class in 32 segments and by two classes in five segments. The differences can be explained by the conditions under which the investigations were performed and by the disparity between a tomographic section and an x ray projection. Magnetic resonance showed 25 segments to have abnormal wall thickness. Only one patient with infarction did not have an area of wall thinning and no patient without infarction had an area of thinning.

It is concluded that magnetic resonance allows an accurate non-invasive assessment of left ventricular wall motion and thickness.

Magnetic resonance allows high resolution tomographic imaging of most organs in the body. Images of static organs, such as the brain and spinal cord, are excellent and these are becoming increasingly valuable in clinical practice. It is possible to produce images of the heart at any point of the cardiac cycle by means of electrocardiographic gating, and image acquisition can be arranged so that flowing blood gives no magnetic resonance signal. This provides high contrast between blood and myocardium without the use of contrast agents and allows the demon-

stration of cardiac anatomy¹⁻³ and both global⁴⁻⁶ and regional ventricular function.⁷ Although other non-invasive techniques such as echocardiography and radionuclide ventriculography can also provide this information, magnetic resonance is particularly versatile because of its high resolution and its ability to image in any plane. In addition, because it can be used to measure blood flow⁸⁻¹⁰ and to study biochemical effects through the relaxation variables T_1 and T_2 ¹¹⁻¹³ and through magnetic resonance spectroscopy,¹⁴ it is likely to be valuable in the investigation of cardiovascular disease.

We have used magnetic resonance to assess regional left ventricular wall motion and have compared these findings with those of x ray ventriculography. We also investigated the relation between wall motion and thickness, another indicator of regional function.

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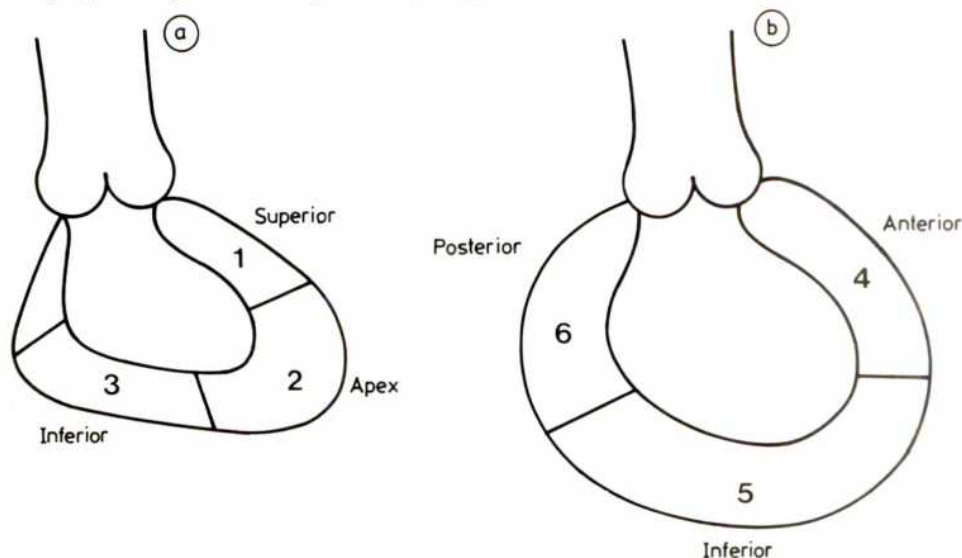


Fig 1 Segmentation of the coronal (a) and sagittal (b) magnetic resonance images and the anteroposterior (a) and lateral (b) ventriculograms for the analysis of wall motion and thickness.

Patients and methods

PATIENTS

We studied 18 patients (17 men and one woman, mean age 52, range 28 to 72). Nine had had a myocardial infarction (diagnosis by history and electrocardiography); four had coronary artery disease without infarction; one had congestive cardiomyopathy (possibly alcoholic); one had rheumatic mitral stenosis; one an atrial septal defect; and two had chest pain, but investigations (including coronary arteriography) had not shown cardiac abnormality.

MAGNETIC RESONANCE

Magnetic resonance images were acquired with a Picker International superconducting machine operating at 0.24 T. The images were reconstructed by two dimensional Fourier transformation of two averages of 128 spin echo sequences with an echo time of 40 ms, so that the acquisition time of each image was between 3 and 4 minutes depending upon heart rate. Coronal images were acquired through the centre of the aortic valve, and sagittal and transverse images were acquired in the planes of widest vertical and lateral diameters of the left ventricular cavity respectively. In each plane an end diastolic image was acquired immediately after the R wave of the electrocardiogram and an end systolic image was timed to coincide with the second heart sound. Tracings of the left ventricular endocardium at diastole and systole were superimposed and divided

into three segments in each plane (fig 1). Wall motion in each segment was classified as normal, hypokinetic, akinetic, or dyskinetic by two independent observers (SRU and RHK) without knowledge of the ventriculographic findings. Wall thickness was also measured to the nearest 0.25 mm by means of dividers and a vernier scale. Abnormality was defined by two different criteria: firstly, if a systolic segment was <75% of the mean of the thickness of neighbouring segments, and secondly if thickness failed to increase between diastole and systole by >25% of the diastolic measurement.

X RAY VENTRICULOGRAPHY

The coronal images were compared with the end diastolic and end systolic frames of an anteroposterior x ray left ventriculogram, and the sagittal images were compared with a lateral ventriculogram. Transverse images were not used in the ven-

Table 1 Number of segments in each magnetic resonance wall motion class and the numbers in which there was disagreement with ventriculography by one and two classes

	Total segments	Disagree by 1 class	Disagree by 2 classes
Normal	63	16	1
Hypokinetic	21	10	0
Akinetic	17	6	3
Dyskinetic	4	0	1
Total	105	32 (30%)	5 (5%)

Table 2 Number of segments according to magnetic resonance wall motion class in the patients with and without previous infarction

	No infarction (9 patients)	Infarction (9 patients)
Normal	46	17
Hypokinetic	6	17
Akinetic	1	16
Dyskinetic	1	4
Total	54	54

$\chi^2 = 33.64$, $p < 0.001$.

triculographic comparison. A cycle was chosen early after injection but remote from extrasystoles, and wall motion was analysed from the angiograms in a similar manner to the magnetic resonance images (observers RSOR and SRU).

Results

WALL MOTION

The wall motion of 105 segments was analysed; one

lateral ventriculogram was uninterpretable. The observers assigned the same wall motion class in 93 segments of the magnetic resonance images, but differed by one class in 11 segments, and by two classes in one segment. For the ventriculograms they agreed in 88 segments and disagreed by one class in 15 segments, and by two classes in two segments. These discrepancies arose principally because of different segmentation of the left ventricular contours and were settled by collaboration.

Table 1 shows the number of segments in each magnetic resonance wall motion class, and the numbers in which there was disagreement by one and two classes when compared with ventriculography. In no segment was there disagreement by three classes. Of the five segments with disagreement by two classes, three were in patients with previous infarction; in these patients magnetic resonance showed akinesis and wall thinning but ventriculography showed normal motion. The fourth was in a patient with coronary artery disease without infarction in whom magnetic resonance showed normal wall motion and thickness but ventriculography

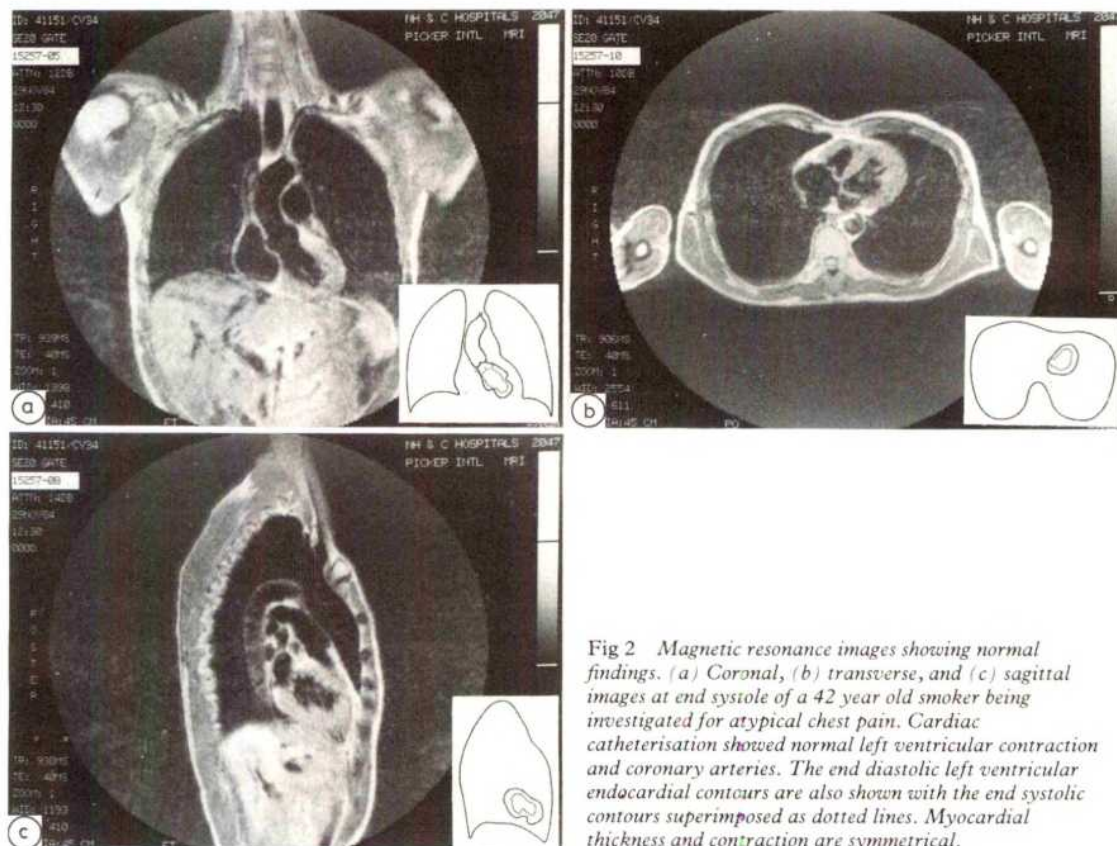


Fig 2 Magnetic resonance images showing normal findings. (a) Coronal, (b) transverse, and (c) sagittal images at end systole of a 42 year old smoker being investigated for atypical chest pain. Cardiac catheterisation showed normal left ventricular contraction and coronary arteries. The end diastolic left ventricular endocardial contours are also shown with the end systolic contours superimposed as dotted lines. Myocardial thickness and contraction are symmetrical.

	(a) Thin	(b) Failure to increase	(a) Alone	(b) Alone
Normal	3	5	0	2
Hypokinetic	5	7	1	3
Akinetic	11	11	1	1
Dyskinetic	2	2	0	0
Total	21	25	2	6



Fig 3 Magnetic resonance image showing anterior infarction. End systolic sagittal image of a 57 year old man with a six year history of angina with anterior infarction four years previously. Cardiac catheterisation showed anterior and apical akinesis with three vessel disease and an occluded left anterior descending artery. There is anterior thinning and akinesis and the transverse images showed that this extended to the septum.

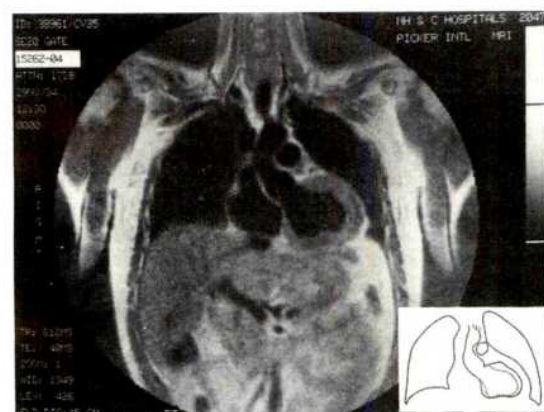


Fig 4 Magnetic resonance image showing inferior infarction. A 45 year old man with inferior infarction two years previously and continuing angina of effort. Cardiac catheterisation showed inferior akinesis and severe three vessel disease with a 90% stenosis of a dominant right coronary artery. The end systolic coronal magnetic resonance image shows inferior wall thinning and akinesis.

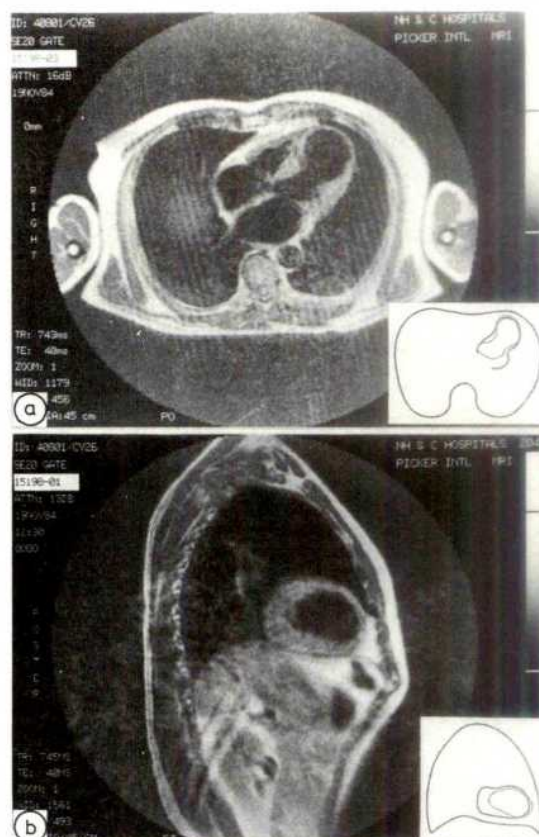


Fig 5 Magnetic resonance image showing left ventricular aneurysm. (a) Transverse and (b) sagittal end systolic images of a 51 year old man with previous anterior infarction. Cardiac catheterisation showed single vessel disease with an occluded left anterior descending artery and an antero-apical aneurysm.

showed akinesia. The fifth was in the patient with atrial septal defect. Magnetic resonance showed paradoxical septal motion. This was also seen by echocardiography; however, ventriculography showed hypokinesis.

Table 2 shows the distribution of magnetic resonance wall motion classes in the patients with and those without previous infarction. All patients with previous infarction had at least one akinetic or dyskinetic segment, whereas only two patients without infarction had these abnormalities. One was the patient with atrial septal defect and paradoxical septal motion and the other was the patient with congestive cardiomyopathy. The presence of akinesis or dyskinesia was therefore a sensitive although not specific indicator of previous infarction.

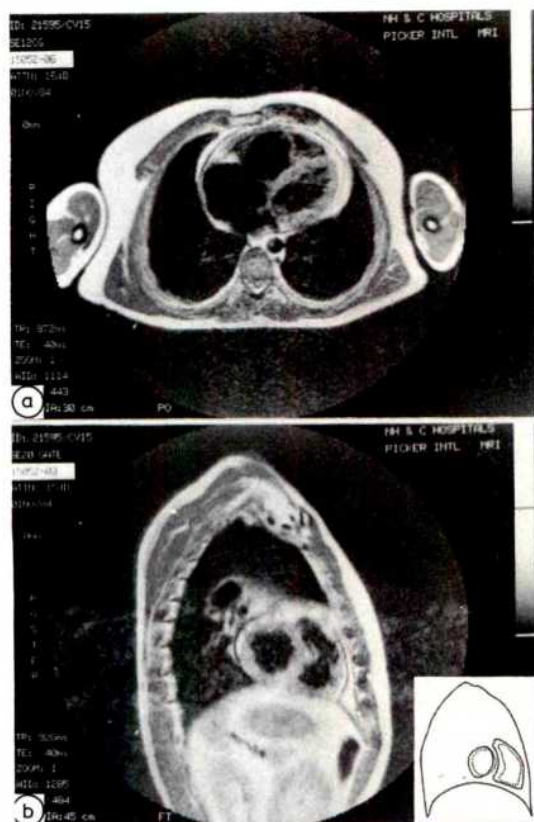


Fig 6 Magnetic resonance image showing atrial septal defect. (a) Diastolic transverse and (b) systolic sagittal images of a 28 year old man with an atrial septal defect. An ostium secundum defect is seen in the transverse image and the right heart is dilated. The sagittal contours show paradoxical septal motion caused by the hyperkinetic right ventricle. Stroke volume measurements from the magnetic resonance images showed the pulmonary to systemic flow ratio to be 2.3 to 1.²⁵

WALL THICKNESS

Twenty one segments were abnormal by the first criterion ($< 75\%$ of the mean of the thickness of adjacent segments at end systole), and in only two of these was there a normal increase in thickness between diastole and systole. Twenty five segments were abnormal by the second criterion (failure to increase in thickness by more than 25% between diastole and systole), and six of these were of normal systolic thickness. Thus although both criteria of abnormal wall thickness usually occurred together, either could occur alone. Both abnormalities were seen only in patients with previous infarction, but one patient who had had an inferior infarction three months previously did not have any abnormality of wall thickness. No patient without previous

infarction had abnormal wall thickness by either criterion.

Table 3 shows the wall motion classes in the segments with abnormal thickness. Although most abnormal segments were either dyskinetic or akinetic, a considerable number were hypokinetic or had normal motion.

Figures 2 to 6 show examples of magnetic resonance images from patients with various conditions.

Discussion

The results show that there is good agreement between magnetic resonance and ventriculography in the assessment of left ventricular wall motion, with important disagreement (more than one class) occurring in only 5% of segments. The technique of x ray contrast ventriculography is often used as a standard by which newer techniques are judged, but in any such comparison it is important to be aware of differences in the techniques that will lead to disagreement. Disagreements may be either real or artefactual. Real disagreements arise because of the relatively invasive nature of ventriculography. Haemodynamic function is altered and the effects of rapid injection of contrast medium are variable.^{15 16} It is possible for instance that the rapid injection of contrast in the patient with atrial septal defect created a temporary left sided volume overload, so that the septum moved as part of the left ventricle rather than paradoxically, as was seen by magnetic resonance in the resting state with right ventricular overload. Artefactual disagreements arise because x ray ventriculography produces a planar projection of the ventricle whereas magnetic resonance produces a tomographic section. This means that the two techniques may not demonstrate the same part of the ventricular wall, because the plane of the ventriculographic outline may be oblique when compared with the plane of the magnetic resonance section (fig 7). In addition, the degree of obliqueness may vary throughout the cardiac cycle.

Another potential source of disagreement arises from the semiquantitative way in which wall motion was assessed. This type of assessment was deliberate since the two techniques are sufficiently different to make more precise quantitative agreement unlikely. It was only the ability to detect and categorise abnormality that was being tested. The classification of wall motion as normal, hypokinetic, akinetic, and dyskinetic is in widespread clinical use, and whereas observers often differ by one category they are unlikely to differ by more. The extent of agreement between the two observers for either ventriculography or magnetic resonance is a measure of the validity of the method being examined.

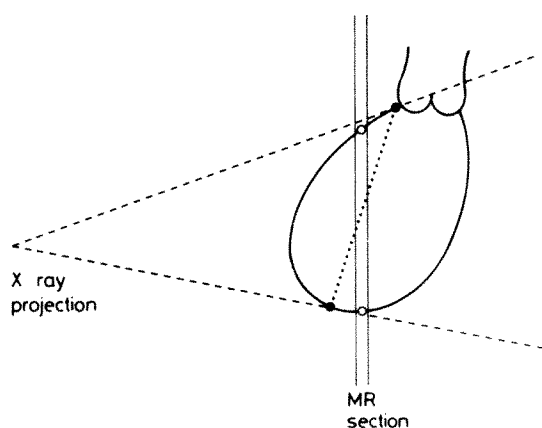


Fig 7 The ventricular wall forming the borders of the x ray ventriculogram may not correspond to that of the tomographic magnetic resonance image.

Magnetic resonance measurements of wall thickness have been shown to be accurate⁴ and previously established normal values were used to define the criteria of normality in this study.^{6,7} Our results show that wall thickness as well as motion is sensitive in the detection of previous infarction but both abnormalities do not always occur together. Since wall motion may also be caused by factors other than myocardial contraction, this is not surprising. Both criteria of abnormal wall thickness usually occurred together, but the thickness of six segments failed to increase between diastole and systole despite their not being thinner than neighbouring segments at systole; this may have been because the neighbouring segments were not necessarily normal. We did not examine how soon wall thinning occurred after infarction but the patient with the most recent infarct (three months) had normal wall thickness. It is likely that failure to thicken during systole will be an early finding and diastolic thinning a later one. Although the wall thickness measurements were sensitive for previous infarction, they are not likely to be specific because patients with non-coronary myocardial disease may also have wall thinning.

We did not attempt to compare the location of abnormalities with the electrocardiographic site of infarction because in the planes that we used the ventricular borders did not correspond to an easily defined wall. Oblique images parallel to the long axis of the left ventricle can now be acquired and are the preferred planes for ventricular volume studies and for wall motion and thickness.¹⁷⁻¹⁹ At the time of this study, our machine, in common with many others, was not able to acquire oblique images. The use of coronal and sagittal planes may explain some

of the unexpected findings because the ventricular wall will not necessarily pass perpendicularly through the image plane.

A full description of regional function cannot be obtained from single tomographic sections and it is difficult to interpret the large numbers of images from multiple sections. There are already techniques to reduce several tomographic images to a single image displaying three dimensional data and a single parametric image showing motion of all parts of the ventricle may be created from a series of short axis sections of the ventricle.²⁰ Magnetic resonance may be used in the future to produce parametric images that show not only wall motion and thickness but also other variables such as rates and timing of contraction. Timing is an important feature of regional ventricular function and abnormal areas may contract later than normal.²¹ This will introduce inaccuracies into measurements made from a single systolic image but cine imaging will avoid this.²²⁻²⁴

Conclusion

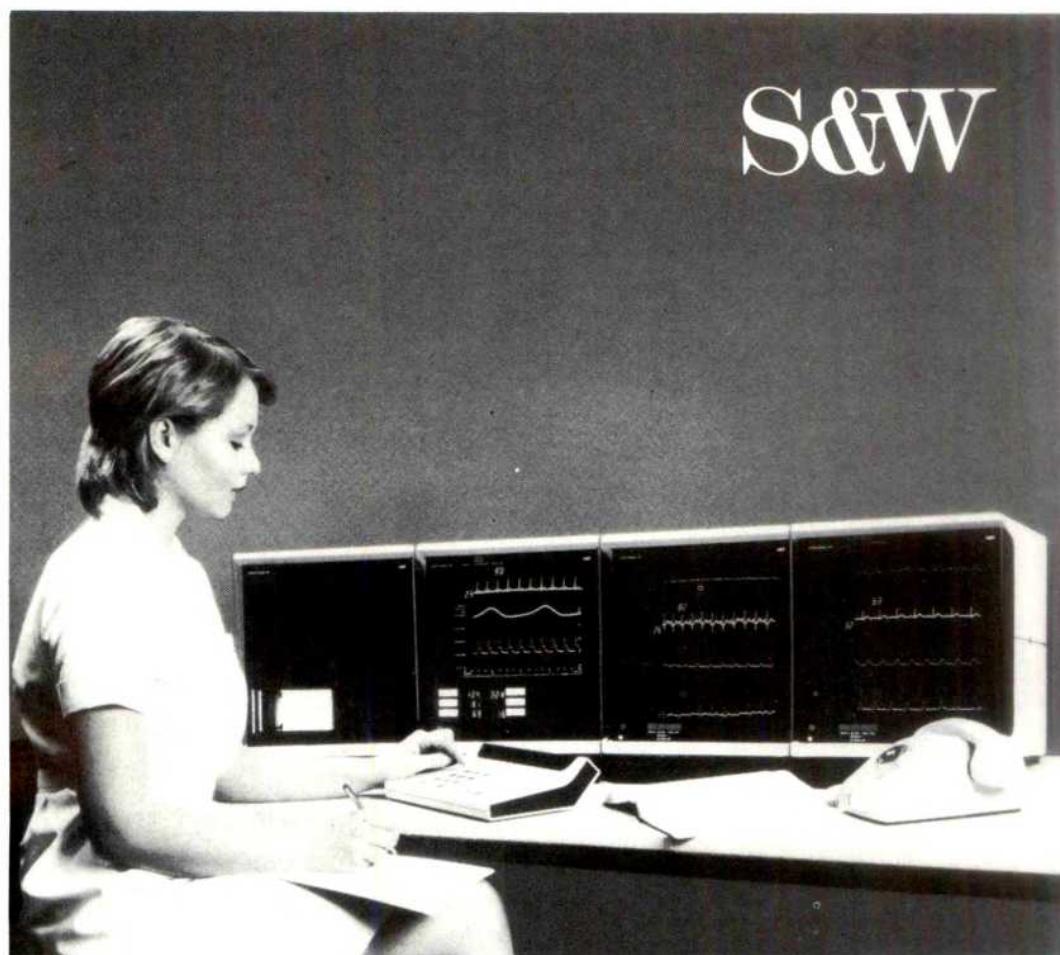
Accurate non-invasive assessment of regional left ventricular function is possible with magnetic resonance. The ability to demonstrate cardiac anatomy and global function and the potential for the measurement of blood flow and the provision of biochemical information suggest that it will become an important technique in the investigation of patients with cardiovascular disease.

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Influence of a variant angina on the results of percutaneous transluminal coronary angioplasty

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SUMMARY Nineteen (86%) of 22 patients with variant angina and important coronary stenoses (>60%) had successful percutaneous transluminal coronary angioplasty. The acute complications in two patients were not caused by coronary spasms but by dissection with disturbance of perfusion. One of these two patients required a coronary bypass graft; the other was treated conservatively. Myocardial infarction developed in both patients. Despite long term administration of nifedipine (30-80 mg daily), restenoses occurred within six months (on average after 10 weeks) in nine patients with symptoms and one without. In four patients the restenoses exceeded the degree of stenosis before angioplasty. Five patients were revascularised by surgical means. Vessels in three out of four patients were later successfully dilated. After a mean period of observation of 24 months (6-51 months) 18 of the 19 patients are symptom free and do not require medication.

The results confirm that angioplasty is an effective method of treating patients with variant angina and important coronary stenoses. The problem of the high frequency of restenosis, however, remains unresolved.

Coronary spasm is important in the various ischaemic syndromes that occur in coronary heart disease.¹⁻³ The clinical spectrum ranges from exercise induced spasm to angina occurring exclusively at rest. Angiography shows normal to very considerably stenosed coronary vessels.^{3,4}

Patients with coronary spasms are usually successfully treated with calcium antagonists.⁵ The results of medical treatment are excellent when the vasospastic component predominates.^{4,6} Revascularisation must be considered, however, in patients with considerable stenoses.^{4,7,8} Some centres report good results with bypass surgery in variant angina^{8,9}; others do not^{10,11} or they recommend plexectomy in addition.⁷

Percutaneous transluminal coronary angioplasty is a method of revascularisation that only slightly inconveniences the patient.¹² Angioplasty has so far been regarded as dangerous or indeed as contraindicated in patients with vasospastic angina because of the danger of intensifying the tendency to spasm

by mechanical irritation and because it is assumed that spasms will continue to cause anginal symptoms despite elimination of the organic stenosis.^{13,14} When there are important fixed stenosis, however, slight spasm could produce constriction leading to a perfusion defect.^{15,16} For this reason we have studied the success rate of angioplasty carried out because of critical coronary stenoses in patients with superimposed coronary spasm caused by variant angina. We report on the short term and long term results in 22 patients.

Patients and methods

Percutaneous transluminal coronary angioplasty was carried out in 265 patients from November 1980 to April 1985. In 22 (8%) patients variant angina had been diagnosed before the procedure. Variant angina was defined as a spontaneous attack of angina pectoris with reversible ST segment elevation (>0.1 mV) without an increase in the concentrations of cardiac enzymes. Patients with impending infarct expansion were not included in this study. In 21 patients, the diagnosis could be made during the spontaneous pain attack in the 12 lead electrocardiogram and in one patient by positive

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ergometrine maleate provocation during diagnostic coronary angiography. Table 1 gives the clinical data on these patients.

Table 1 Clinical data

Data	No
Total patients	22
Male/female	15/7
Mean (SD) age (yr) (range)	52 (11) (33-74)
Duration of angina (weeks)	6 (12)
No with angina for <6 weeks	17
Previous myocardial infarction	3
Rest angina	22
Exertion angina	19
ST segment elevation	
Anterior	15
Inferior	7
Single vessel disease	22
Results of medical treatment	
Symptom free	0
Improved	10
Unchanged	12

Bicycle ergometry and thallium-201 scintigraphy were carried out in seven patients before and after successful angioplasty. In eight additional patients these investigations were performed only in the first week after successful angioplasty. Coronary angiography was performed by Judkins's technique. The degree of fixed coronary stenosis was calculated before and after angioplasty (after sublingual glyceryl trinitrate (0.8 mg) and nifedipine (10 mg) had been given) as a mean reduction of diameter in at least two projections in end diastole. The degree of stenosis was measured independently by two of the authors using a calibrated magnifying glass.¹⁷ The same projections were always used in comparison investigations and the same vasodilators were administered to assess the degree of stenosis at follow up angiography.

DETECTION OF CORONARY SPASM

Spontaneous spasm was seen at diagnostic coronary angiography in three patients during an attack of variant angina. In nine patients we attempted to provoke spasm with serial doses of ergometrine maleate (from 0.05 mg to a maximum of 0.2 mg). This provoked a positive result in seven patients but not in two. The ergometrine maleate test was deemed to be positive if it led to a complete coronary occlusion or a considerable increase in the degree of stenosis (>20%) with anginal symptoms or ischaemic changes in the electrocardiogram or both. The ergometrine maleate provocation test was not used in the remaining 10 patients because they had severe clinical symptoms with several attacks each day.

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Angioplasty was indicated in all patients because of

important coronary stenosis (>60%) with treatment resistant angina pectoris. The procedure was carried out in accordance with the method developed by Gruentzig *et al* with surgical standby.¹² After angioplasty all patients were monitored for 24 hours and the standard electrocardiogram and the heart muscle specific enzymes (NAC-creatine kinase and creatine kinase MB) were checked every six hours.

All patients received 40-80 mg isosorbide dinitrate and 40-80 mg nifedipine daily and three patients also received 40 mg propranolol three times a day. Patients were also treated with aspirin (1.5 g/day) beginning on the day before angioplasty and with 10 mg diazepam and 20 mg nifedipine two hours before angioplasty. An infusion of glyceryl trinitrate (1-2-3.0 mg/h) was started before angioplasty and was continued for 24 hours.

During angioplasty heparin (10 000 units), low molecular weight dextran, and intracoronary glyceryl trinitrate (0.2-0.4 mg) were given. After angioplasty and up to the planned follow up angiography all patients were given 30-80 mg nifedipine daily and 14 patients also received isosorbide dinitrate (40-80 mg). Patients 1-5 received warfarin and the remainder took 0.5 g of aspirin daily.

FOLLOW UP

All patients were discharged two to three days after a successful angioplasty, and they were asked to attend again after six months for an angiographic examination. The follow up examination was done earlier if angina recurred. In the subsequent years the patients were followed up every six months.

Results

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Angioplasty was successful (producing a >20% widening of the stenosis) in 19 (86%) out of 22 patients (table 2). Double stenoses in the left anterior descending artery or of the circumflex artery were dilated in two patients. The mean (SD) degree of stenosis was reduced from 80 (10)% to 30 (15)%, and the transstenotic systolic pressure gradient from 66 (15) mm Hg to 19 (9) mm Hg. In one patient with a severe stenosis in the left anterior descending artery, the stenosis could not be passed with the bal-

Table 2 Results of angioplasty

	No	%
Successful angioplasty	19/22	(86)
Left anterior descending artery	13/15	(87)
Right coronary artery	4/5	(80)
Circumflex artery	2/2	(100)

loon. In two patients with stenosis in the proximal region of the right coronary artery, angioplasty led to dissection in the stenotic region with deterioration of perfusion and signs of ischaemia (chest pain, ST segment elevation). One patient suffered a complete occlusion and was immediately operated on, and the other patient who had maintained residual perfusion was treated conservatively. Both patients had a myocardial infarction, however. During angioplasty three patients had occlusive spasms in the stenotic region. These resolved again immediately after a repeat intracoronary dose of glyceryl trinitrate. A further patient had chest pain lasting for three hours but there was no objective evidence of ischaemia.

BICYCLE ERGOMETRY AND THALLIUM-201 SCINTIGRAPHY

Two of the seven patients investigated by ergometry before angioplasty had normal exercise tolerance (150 or 175 W), but five patients were restricted to 75 W by angina pectoris. Three patients showed exercise induced ST segment elevation and four patients showed ST segment depression. All patients had reversible thallium-201 defects in the area supplied by the stenosed coronary artery.

Immediately after the successful angioplasty reversible thallium defects were no longer seen in any of the seven patients who were tested before angioplasty. One patient continued to show ST segment depression and a further patient showed a normalisation of negative T waves. None of the patients had angina pectoris and their mean (SD) exercise tolerance rose from 100 (50) W to 133 (26) W.

After successful angioplasty the remaining eight patients could carry out an average of 115 (23) W exercise without angina developing. Two patients had ST segment depression but no patient had reversible ischaemia shown by the thallium-201 scintigram.

ANGIOGRAPHIC FOLLOW UP (TABLE 3)

All 19 patients in whom dilatation was successful were examined by angiography within six months. In eight patients the investigation had to be carried out before six months had elapsed because they had both rest and exercise angina 4–20 weeks (mean 10 weeks) after angioplasty. All eight patients showed a restenosis (>50% restenosis). In four patients the restenosis was more severe (>90%) than the original stenosis. Two of these patients had a complete coronary occlusion. None of the patients had sustained a myocardial infarction, because there was a good collateral supply. In four patients the restenosis was equivalent to that found before angioplasty.

At a routine 6 month follow up 10 patients were

symptom free and one patient had angina on exertion with occasional attacks at rest. The symptomatic patient and one symptom free patient had restenoses equivalent to the stenosis present before angioplasty. Nine symptom free patients did not show any restenosis. The rate of restenosis determined angiographically within six months was 53% (10/19).

Table 3 Recurrence after angioplasty

	No
Restenoses (<6 months):	10 (53%)
Symptomatic	9
Asymptomatic	1
More severe than before angioplasty	4
Repeat angioplasty (successful)	3/4
Coronary bypass surgery	5
No restenoses (asymptomatic)	9

FOLLOW UP OBSERVATION (TABLE 3)

Four patients with severe restenoses and one patient with restenosis and aneurysm in the dilated region of the coronary artery had coronary bypass surgery within 6 months of angioplasty. Two patients had a perioperative myocardial infarction. A further four symptom free patients with restenosis had repeat angioplasty, which was successful in three patients. The patient in whom dilatation was not achieved was treated conservatively. One further patient with restenosis was also symptom free and off medication.

After a mean observation period of 24 months (6–51 months), 18 out of 19 patients with successful primary dilatation were symptom free and off medication: nine patients without restenosis, one patient with restenosis, five patients after bypass surgery, and three patients after repeat angioplasty. The remaining patient, with restenosis, is in New York Heart Association stage II.

Discussion

Although percutaneous transluminal coronary angioplasty is widely used to treat coronary stenoses irrespective of the clinical coronary syndrome, there are few reports of its use in patients with coronary stenosis and vasospastic angina.^{18–20} Corcos *et al* reported on 21 patients with variant angina in whom the diagnosis was made only after angioplasty in one third of the cases²⁰; however, variant angina was diagnosed before dilatation in the study of Bertrand *et al*¹⁹ and in our 22 patients. Despite full medical treatment (isosorbide dinitrate, nifedipine), all our patients had symptoms: in 12 recurrent spontaneous attacks with ST segment elevation had continued and in 10 there had been a clinical improvement but they were not free of symptoms:

The primary success rates of angioplasty in patients with variant angina are excellent and indeed they are better than the short term results reported in consecutive series.²⁰ Dilatation was successful in 19 (86%) of our 22 patients, whereas our primary success rate in the remaining 243 dilated patients was 72%. Clinically important coronary spasm was seen during angioplasty in about 5% of cases.²¹ Very occasionally coronary spasm led to myocardial infarction or made it necessary to carry out emergency bypass surgery.²² Hence angioplasty in patients with coronary stenoses and superimposed coronary spasm appeared to be especially risky. Initial experience in a few cases, however, did not confirm that the immediate risk in these patients was increased,^{18 23 24} and these results were confirmed in larger numbers of patients.^{19 20}

Although coronary spasms occurred in three of our patients during angioplasty, the complications we encountered were not caused by coronary spasms. In two patients there was a persistent disorder of perfusion caused by dissection. In one case this necessitated emergency bypass surgery and in another patient it led to a myocardial infarction. Others have not reported higher rates of complications.^{18 20 25} Restenoses were reported in 13% and 34% of two large series.^{26 27} Known risk factors for restenosis include male sex, severe symptoms before angioplasty, no history of myocardial infarction, a long stenosis, and a persistent transstenotic pressure gradient of > 15 mm Hg.^{27 28}

Particularly high rates of restenosis have been reported in patients with variant angina. Corcos *et al* reported restenosis in nine (47%) out of 19 patients²⁰ and Bertrand *et al* reported it in 13 (40%) out of 32.¹⁹ We found restenosis at angiographic examination within six months of angioplasty in all nine patients with symptoms (eight patients with resting and exercise angina, one patient with exercise angina only) and in one symptom free patient. The rate of restenosis in these patients is more than twice that at angiographic follow up of 118 patients with stable angina (21%). Coronary spasm alone without restenosis was not the cause of the anginal symptoms which occurred after a symptom free interval of 2–12 weeks after angioplasty in patients with symptoms. The development of more severe obstruction than had been present before angioplasty within a few weeks in four of our patients suggests that the progression of a stenosis may be accelerated by angioplasty. We do not know to what extent the stenosis would have progressed without angioplasty or whether vasospasms can be provoked by the dilatation itself.

Current experience indicates that coronary spasm rarely occurs after angioplasty in patients without

variant angina^{20 29} and is not a major risk factor for restenosis.³⁰ The higher frequency of restenosis and the brief occurrence of anginal symptoms after angioplasty in patients with variant angina suggest that in some cases spasm may favour the development of a restenosis. Our study does not allow us to confirm or deny the observation of Corcos *et al* that the restenosis rate can be significantly reduced by longer term administration of calcium antagonists.²⁰ In our series the incidence of restenoses was 53% despite long term nifedipine treatment (30 to 80 mg daily). In a similar study group Corcos *et al* found that in 14 patients receiving diltiazem (120 mg three times daily) after angioplasty the restenosis rate was only 21% (3/14).²⁰ This difference may reflect the efficacy of the two calcium antagonists and the more severe clinical course in our patients.

Patients with variant angina have a high frequency of myocardial infarction and death in the acute phase.³ Although the outcome of patients with variant angina on appropriate treatment is reasonably good after the acute phase, even in the presence of severe coronary atherosclerosis,^{31 32} only about 50% of the patients remained symptom free for at least one year.³¹ Angioplasty produced more of an improvement in symptoms than medical treatment alone, but we cannot compare the prognosis of patients with variant angina in the two treatment groups because the numbers of patients were small. Eighteen of our 19 patients were symptom free 24 months after angioplasty and six months after the discontinuation of calcium antagonists. Nine did not have restenosis, one had restenosis, five had had bypass surgery, and three had had repeat angioplasty. The remaining patient, with restenosis, has slight symptoms (New York Heart Association group II).

Corcos *et al* also found that patients with variant angina had a favourable medium term course after angioplasty.²⁰ Within a mean observation period of 33 months there was one death and the 20 other patients were symptom free (three after bypass surgery, five after repeat angioplasty, and two on continuing calcium antagonists).

Although coronary angioplasty made a large percentage of patients symptom free, the most effective drug treatment after angioplasty in patients with variant angina remains to be determined. The value of administering higher doses of calcium antagonists must be tested in a controlled study.

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Nocturnal angina: precipitating factors in patients with coronary artery disease and those with variant angina

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SUMMARY Factors precipitating nocturnal myocardial ischaemia were investigated in 10 patients with frequent daytime and nocturnal angina pectoris. Eight patients had fixed obstructive coronary artery disease or a low exercise threshold or both before the onset of ischaemia. Two patients had variant angina with normal coronary arteries and negative exercise tests. During sleep the electrocardiogram, electroencephalogram, electro-oculogram, electromyogram, chest wall movements, nasal airflow, and oxygen saturation were continuously measured. Forty two episodes of transient ST segment depression were recorded in the eight patients with coronary artery disease and 26 episodes of ST segment depression and elevation in the two patients with variant angina and normal coronary arteries. All episodes of ST segment depression in the former group of patients were preceded by an increase in heart rate as a result of arousal and lightening of sleep, bodily movements, rapid eye movement sleep, or sleep apnoea (one episode). In contrast, in the variant angina group no increase in heart rate, arousal, or apnoea preceded 23 of the 26 episodes of ST segment change. Thus increase in myocardial oxygen demand was important in precipitating nocturnal angina in patients with coronary artery disease and reduced coronary reserve. In the patients with coronary spasm these factors did not often precede the onset of nocturnal myocardial ischaemia.

Angina usually occurs on exertion during the day and is regarded as being secondary to an increase in myocardial oxygen demand that cannot be met by a simultaneous increase in blood flow because of obstructive coronary artery disease. It can also occur at rest and during sleep at night. The occurrence of nocturnal angina in patients with daytime pain was recognised in one of the earliest descriptions of the syndrome by Heberden.¹ The suggestion that coronary artery spasm was a possible mechanism of angina pectoris,² did not receive widespread support until Prinzmetal *et al* described the classic symptoms in patients with normal coronary arteries.³ Much more clinical, haemodynamic, and angiographic evidence has been accumulated in these patients that

supports coronary artery spasm as the underlying pathophysiological mechanism.^{4,5} It has been suggested, on the basis of these results, that even the nocturnal angina that occurs in patients with fixed obstructive coronary artery disease is secondary to coronary spasm or sudden reductions in coronary blood flow.^{6,7}

Episodes of ST segment depression and elevation, which may or may not be associated with chest pain, can be recorded by ambulatory electrocardiographic monitoring.⁸ In a preliminary study we examined the momentary changes in heart rate that preceded or accompanied episodes of nocturnal ST segment depression in patients with severe obstructive coronary artery disease.⁹ This detailed analysis showed that there was invariably a small but important increase in heart rate before the onset of ST segment depression in both painful and pain free nocturnal episodes. To evaluate further the mechanisms underlying nocturnal angina pectoris we have performed all night polygraphic studies in this group of

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patients and have compared their results with those of patients with normal coronary arteries and angiographically proven coronary spasm.

Patients and methods

PATIENTS

We studied six men and four women (aged 46 to 79 years) with frequent nocturnal and daytime angina pectoris that was associated with reversible ST segment changes. Patients 1–8 had a very low exercise threshold before ST segment depression occurred (mean (SD) 2.9 (1.4) min) during treadmill stress testing with a modified Bruce protocol. Severe three vessel coronary artery disease (>70% coronary luminal narrowing) was demonstrable in five patients at angiography and at necropsy in one; one patient had a severe proximal left anterior descending artery stenosis only. The 79 year old patient did not have cardiac catheterisation. Patients 9 and 10 had a negative exercise test and no important coronary artery disease at angiography. Provocation with ergometrine maleate (mean dose 0.1 mg) during coronary angiography produced considerable localised spasm in a single coronary artery in both patients, which was accompanied by chest pain and ST segment elevation on the electrocardiogram.

STUDY PROTOCOL

Patients were weaned off all antianginal medication before the sleep studies. Glyceryl trinitrate was used to treat painful episodes. Polygraphic recordings were made during nocturnal sleep for one night in six patients and for two consecutive nights in four patients (mean (SD) 9 (3) hours (range 6–13 hours)). Informed consent was obtained from all patients and the study was approved by the hospital ethics committee.

POLYGRAPHIC RECORDINGS

We obtained continuous overnight recordings of the electrocardiogram, electroencephalogram (C4/A1 or C3/A2 or both), electro-oculogram (two channels), and submental electromyogram. An ear oximeter (Hewlett Packard) was used to measure arterial oxygen saturation, nasal airflow was measured with a

thermistor, and chest wall movements with an impedance pneumogram. Patients slept in a sound reduced room and were observed by one of us throughout each study. Recordings of all observations were obtained on an eight channel ink jet recorder (Siemens, Mingograph) which was run at 15 mm/s. Recordings of arterial oxygen saturation, chest wall movements, and nasal airflow were also obtained on a separate four channel paper recorder (Hewlett-Packard) run at 25 mm/min. Sleep was staged by the standard guidelines of Rechtschaffen and Kales.¹⁰

A continuous bipolar electrocardiogram of lead CM5 was obtained on a frequency modulated recorder (Oxford Medilog II) so that the ST segment shifts could be accurately measured. Important ST segment depression was defined as depression of ≥ 1 mm of the ST segment below the isoelectric line 0.08 s after the end of the QRS complex that persisted ≥ 1 min. Important ST segment elevation was defined as a ≥ 1 mm shift upwards of the ST segment at the J point. Changes in the ST segment were measured with a magnifying lens equipped with a graticule, which enabled us to measure to an accuracy of 0.1 mm. This meant that the exact time of onset of the ST segment change could be determined. ST segment shifts that occurred after changes in position were not regarded as important unless the changes returned to normal while the patients remained in the new position or if these episodes were followed by angina. For the purposes of this study isolated T wave changes were not regarded as good indicators of myocardial ischaemia. Careful analysis of the R-R interval was performed for at least 5 min before the onset of ST segment change (baseline heart rate) and was continued throughout the episode. The R-R interval was measured every 6 s to detect precisely the time of onset of any change in heart rate. Thus the exact time of onset of ST segment change and its relation to the change in heart rate could be determined. All the results are expressed as mean (SD).

Results

A total of 90 hours of recording was obtained during 14 nights of sleep in the 10 patients. The eight

Table Frequency and duration of episodes of ST segment change observed during sleep in patients with important coronary artery disease or positive exercise tests (cases 1–8) and patients with coronary spasm (cases 9 and 10)

Cases	Episodes of ST depression	Episodes of ST elevation	Number of painful episodes	Total duration of episodes (min)
1–8	42	0	18	64 (56) (mean (SD))
9	8	6	3	169
10	11	1	2	167

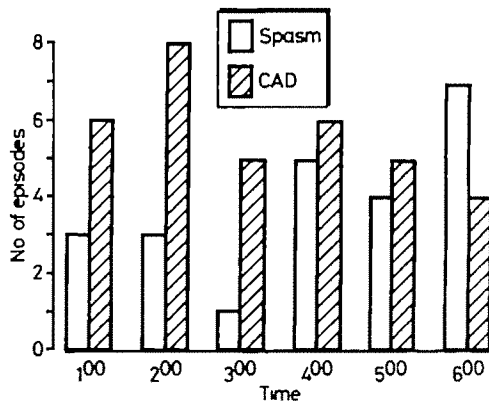


Fig 1 Hourly frequency of episodes of ST segment change in patients with coronary artery disease (CAD) (hatched bars) and patients with normal coronary arteries and spasm (unhatched bars).

patients with obstructive coronary artery disease had 42 episodes of nocturnal ST segment depression (mean 5.3 (3.5), range 1–13) of which 43% were painful, and they lasted from 1 to 81 min (table). In the two patients with normal coronary arteries and spasm there were 26 episodes of transient ST segment change during sleep, 19 with ST segment depression and seven with ST segment elevation. Of these, 19% were painful and they lasted from 2 to 8 min (table).

Episodes of ST segment change were equally distributed throughout the night, with no tendency for episodes to occur in the early morning hours in the eight patients (cases 1–8) with fixed obstructive coronary artery disease. The two patients with coronary spasm (cases 9 and 10) had more episodes of ST segment change lasting for a longer period in the early morning hours (16 episodes lasting 213 min from 4.00–7.00 am) compared with the early part of the night (7 episodes lasting 105 min from 1.00–4.00 am) (fig 1).

RELATION BETWEEN ST SEGMENT CHANGES AND SLEEP STAGES

Patients with coronary artery disease

In the patients (cases 1–8) with obstructive coronary artery disease and strongly positive stress tests most episodes of ST segment depression were preceded by arousal from deeper sleep stages to lighter sleep stages or to awakening; this was followed immediately by an abrupt increase in heart rate (fig 2). Often bodily movements, such as turning, followed the arousal and were associated with further increases in heart rate. Figure 2 shows an example of the onset of one episode of ST segment depression. Thirty nine

Quyyumi, Efthimiou, Quyyumi, Mockus, Spiro, Fox

of the 42 episodes of ST segment depression were preceded by arousal in which the electroencephalogram changed from a high amplitude slow wave pattern to a low amplitude high frequency pattern. This was followed immediately by an increase in heart rate from 68 (10) beats a minute to 87 (10) beats a minute, and only later did the ST segment start to change. All but one of the patients were awakened with chest pain at least once during each night of the study and were given sublingual glyceryl trinitrate.

Four episodes of ST segment depression were associated with rapid eye movement sleep periods. Two episodes followed increases in heart rate which

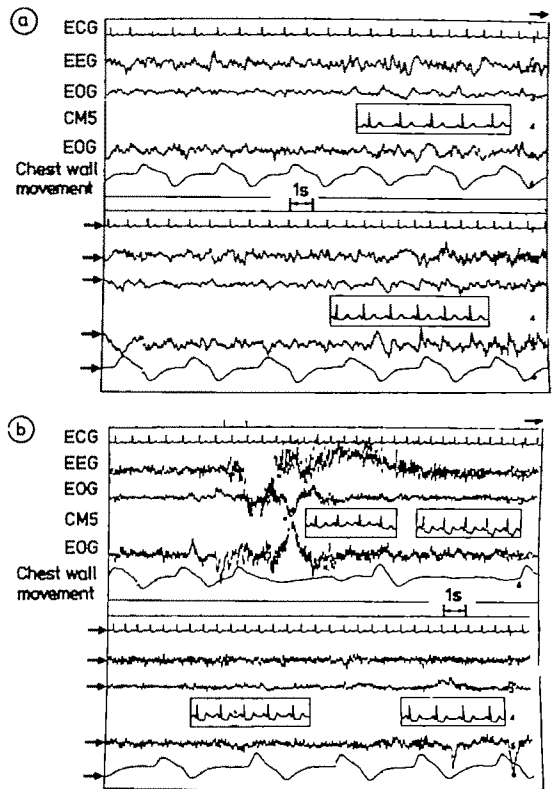


Fig 2 Polygraphic records (a and b) from a 63 year old woman with three vessel coronary artery disease during sleep demonstrating the onset of an episode of ST segment depression. The electroencephalogram (EEG), electrocardiogram (ECG), electro-oculograms (EOG), and chest wall movements were recorded at 15 mm/s. Insets of the electrocardiogram recorded from lead CM5 at 25 mm/s are shown. Sleep stage III followed by sudden arousal to stage I/II was associated with an increase in heart rate. Further increase in heart rate after turning (movement artefact) was followed by the onset of ST segment depression.

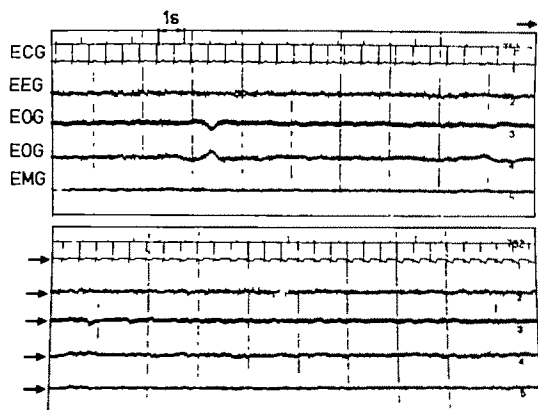


Fig 3 Polygraphic recording from a 58 year old woman with normal coronary arteries and spasm in the left circumflex coronary artery during sleep showing the onset of an episode of ST segment depression. The electrocardiogram (ECG), electroencephalogram (EEG), electro-oculogram (EOG), and electromyogram (EMG) were continuously recorded. There was no change in sleep stage or heart rate before the onset of ST depression.

occurred during the later phases of rapid eye movement sleep. The other episodes occurred when arousal from rapid eye movement sleep to a lighter sleep stage occurred, again preceded by an increase in heart rate. Epoch marking of the electroencephalogram recordings throughout the night showed that all patients spent a proportionately greater time in lighter sleep stages (1, 2, or awake) probably as a result of repeated awakening with chest pain. Rapid eye movement sleep, however, occurred in all patients, lasted for a mean of 44 min each night, and was more prevalent during the second night. On several occasions arousal from deeper sleep stages to lighter sleep occurred and was accompanied by an abrupt increase in heart rate but this was not followed by important ST segment depression (>1 mm) or pain. There was, however, a <1 mm shift in the ST segment. In the absence of another independent marker it is impossible to know whether such changes also constitute ischaemia. In this study we have reported only those episodes of ST segment change that were ≥ 1 mm, although it is likely that smaller changes also represent periods of less severe ischaemia. There were also differences in the baseline heart rate and the magnitude and rate of increase of the heart rate during different episodes of arousal in the same patient.

Patients with coronary artery spasm

Twenty three of the 26 episodes of ST segment change observed in the two patients with spasm were

not preceded by increases in heart rate, changes in sleep stages, or bodily movement (fig 3). Episodes started with an initial change in the T wave vector, progressed to peaking of the T wave and important ST segment elevation, and ended with ST segment depression. There were 19 episodes of ST segment depression and seven episodes of ST segment elevation. In one patient, however, there were three episodes (our of a total of 14) of ST segment depression that were preceded by a lightening of sleep pattern, bodily movement, and increases in heart rate which resembled episodes in patients who had obstructive coronary artery disease.

RELATION BETWEEN NOCTURNAL ST SEGMENT CHANGES AND RESPIRATION

In one patient with three vessel coronary artery disease and episodes of ST segment depression at night, one episode was preceded by central apnoea with cessation of chest wall movements and nasal airflow for 22 s. Oxygen saturation fell from a baseline of 96% to 82% and this was followed by an increase in heart rate and onset of ST segment depression (fig 4). None of the other episodes of ST segment depression or elevation, in this or any other patient, was preceded or accompanied by changes in respiratory pattern or oxygen saturation. This patient had other episodes of ST segment depression that were not preceded by apnoea but occurred as a result of lightening of sleep and bodily movements. He also had further brief episodes of central respiratory depression (fig 4) with reductions in chest wall movement and nasal airflow, but these did not result in a reduction of oxygen saturation or a change in heart rate or the ST segment.

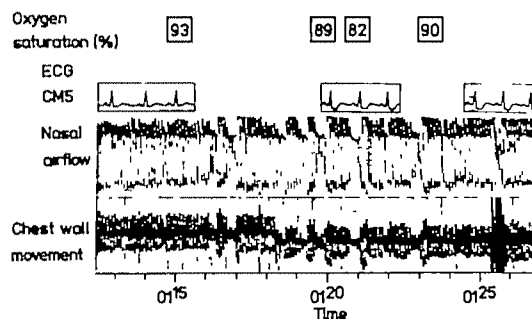


Fig 4 Recordings of the nasal airflow, chest wall movement (25 mm/min), electrocardiogram (25 mm/s), and oxygen saturation during sleep in a 68 year old man with three vessel coronary artery disease demonstrating several brief episodes of central apnoea with the final episode of apnoea lasting 22 s. This was followed by desaturation, increase in heart rate, and ST segment depression.

Discussion

In this study we have examined two distinctly separate groups of patients who had frequent daytime and nocturnal angina pectoris. One group had obstructive coronary artery disease or positive exercise test at a low workload or both, whereas the other group had no important coronary artery disease and had negative exercise tests and localised coronary spasm. Most of the ischaemic episodes of ST segment depression in patients with coronary artery disease were preceded by movement, arousal, and increases in heart rate. We analysed the momentary changes of heart rate that preceded episodes of ST segment change occurring at night in a previous study.⁹ In those patients, all with severe obstructive coronary artery disease, almost all of the episodes of ST segment depression were preceded by small but significant increases in heart rate of the order of 20(12) beats per minute. This study has demonstrated that these increases in heart rate are chiefly a result of arousal and lightening of the sleep phase or are associated with rapid eye movement sleep. Central apnoea occurred in only one subject and though this slightly reduced oxygen saturation (to 82%), there was a sudden increase in heart rate, which possibly was more important in initiating myocardial ischaemia. At other times of the night further episodes of ST segment depression that followed bodily movements and arousal developed in this patient. The occurrence of this degree of sleep apnoea in the symptom free population is believed to be not uncommon, although the true incidence is unknown.¹¹ To our knowledge there is no information on its relation with angina pectoris.

Whereas some studies have shown that episodes of nocturnal ST segment change occurred during the rapid eye movement phase of sleep,¹²⁻¹³ others have reported no relation between rapid eye movement sleep and nocturnal angina.¹⁴⁻¹⁵ Wide fluctuations of heart rate and blood pressure are also known to occur during rapid eye movement sleep as a result of autonomic stimulation.¹⁶⁻¹⁷ In our study, episodes associated with rapid eye movement sleep were uncommon. Analysis of the sleep pattern confirmed that patients spent a proportion of their sleep time in the rapid eye movement phase of sleep. Because patients repeatedly awoke with chest pain several times each night the periods of rapid eye movement associated sleep were short, especially during the first night. We attempted to overcome this difficulty by having four patients sleep for two nights; they had longer periods of rapid eye movement sleep on the second night.

It was not the purpose of this study to establish the sleep pattern of patients with nocturnal angina. This

Quyyumi, Efthimiou, Quyyumi, Mockus, Spiro, Fox

would have required several nights of acclimatisation in the sleep laboratory. This was not acceptable in our patients because they were suffering from frequent angina and were being investigated after withdrawal of all antianginal medication. Lightening of sleep, arousal, and bodily movements are normal during sleep and are followed by an increase in heart rate and blood pressure.¹⁶⁻¹⁷ The magnitude of these haemodynamic changes varies between different episodes of arousal. In this study several episodes of arousal occurred that increased heart rate but were not followed by important ST segment depression (>1 mm). There may be several reasons for this. Firstly, we arbitrarily used 1 mm of ST segment depression as being representative of ischaemia. Often, episodes of heart rate increase were followed by depression of the ST segment that did not reach 1 mm. These may have indicated periods of less severe myocardial ischaemia. Secondly, some episodes of arousal were followed by an increase in heart rate that was less than that which occurred when such arousal was accompanied by bodily movements such as turning. The latter was more likely to result in important ST segment depression. Also a slower arousal or bodily movements may result in a less rapid increase in heart rate which may also influence the development of ischaemia.

Finally, heart rate is just one of the determinants of myocardial oxygen demand. In this study we did not attempt to measure changes in blood pressure and end diastolic volume, which also influence myocardial oxygen demand. It is known that arousal and rapid eye movement sleep are also associated with fluctuations in blood pressure¹⁶⁻¹⁷ and that recumbency increases end diastolic volume. If the magnitude of these changes varied during the course of the night it is not surprising that only some of the episodes of arousal were followed by important ST segment changes.

The size of the increase in heart rate before the onset of ST segment depression in patients with coronary artery disease varied in the same individual at different times of the night. The interval between the heart rate increase and the onset of ST segment depression also varied. This may have been either because differences in the magnitude of the stimulus were causing the change (arousal only versus arousal and turning) or because the magnitude of change in other factors such as blood pressure, end diastolic pressure, or coronary tone varied at different times of the night. Exercise tolerance in these patients was very low. We did not measure the heart rate at the onset of ST segment depression during the exercise tests. The resting heart rate and blood pressure during the daytime are higher than at night and it is therefore difficult to compare the absolute levels of

heart rate or the magnitude of increase in heart rate during the exercise test with the increase that preceded ST segment changes at night.

It is impossible to exclude the influence of alterations in coronary tone,⁶ platelet aggregation,¹⁸ and other factors that may increase the obstruction of the coronary lumen in patients with severe coronary artery disease. Indeed there is evidence that coronary artery tone is higher during the night than during the day^{19,20} and this may predispose patients to the development of ischaemia at lower levels of exertion at night than during the day. The important finding in this study is that in patients with severe coronary artery disease increases in myocardial oxygen demand immediately precede the onset of ischaemia at night as well as during the day.

Continuous haemodynamic monitoring in patients with variant angina has shown that no important changes in heart rate, blood pressure, left ventricular filling pressure, or cardiac output preceded the onset of ST segment changes.^{6,7} In a proportion of patients in whom all night polygraphic studies were performed, ST segment elevation or depression was not associated with rapid eye movement sleep or with any changes in sleep pattern.¹²⁻¹⁴ In the present study episodes of ST segment change developed in two patients with proven coronary artery spasm; most were not preceded by changes in the heart rate, respiratory rate, or oxygen saturation. Episodes were more common during the early morning hours¹⁹ (fig 1). The factors that precipitate coronary artery spasm remain obscure. Coronary artery tone is increased at night and tends to be highest in the early morning hours^{19,20}; this may account for the increased frequency. Although all the episodes in one patient and 11 of the 14 episodes in the other patient were not preceded by increases in heart rate, three episodes of ST segment depression followed arousal and tachycardia. Possibly coronary spasm was partly but not completely occluding the vessel at these times and was not producing myocardial ischaemia under resting conditions. After arousal and an increase in heart rate, myocardial oxygen demand increased and this resulted in ischaemia and onset of ST segment depression.

Most of the episodes of ST segment elevation and depression were not accompanied by chest pain. In individual patients, however, the factors associated with and preceding the onset of painful and pain free episodes of ST segment change were identical. Similarities in haemodynamic and functional variables accompanying painless and painful episodes of ST segment change have been demonstrated before.²¹ The factors that precipitate myocardial ischaemia at rest in patients with obstructive coronary artery dis-

ease and limited coronary reserve differ from those that precipitate ischaemia in patients with normal coronary arteries and spasm. The importance of increased myocardial oxygen demand in the former group of patients has been clearly demonstrated and its therapeutic implications need to be further investigated.

We thank the British Heart Foundation for support and Dr T McMorland for his assistance.

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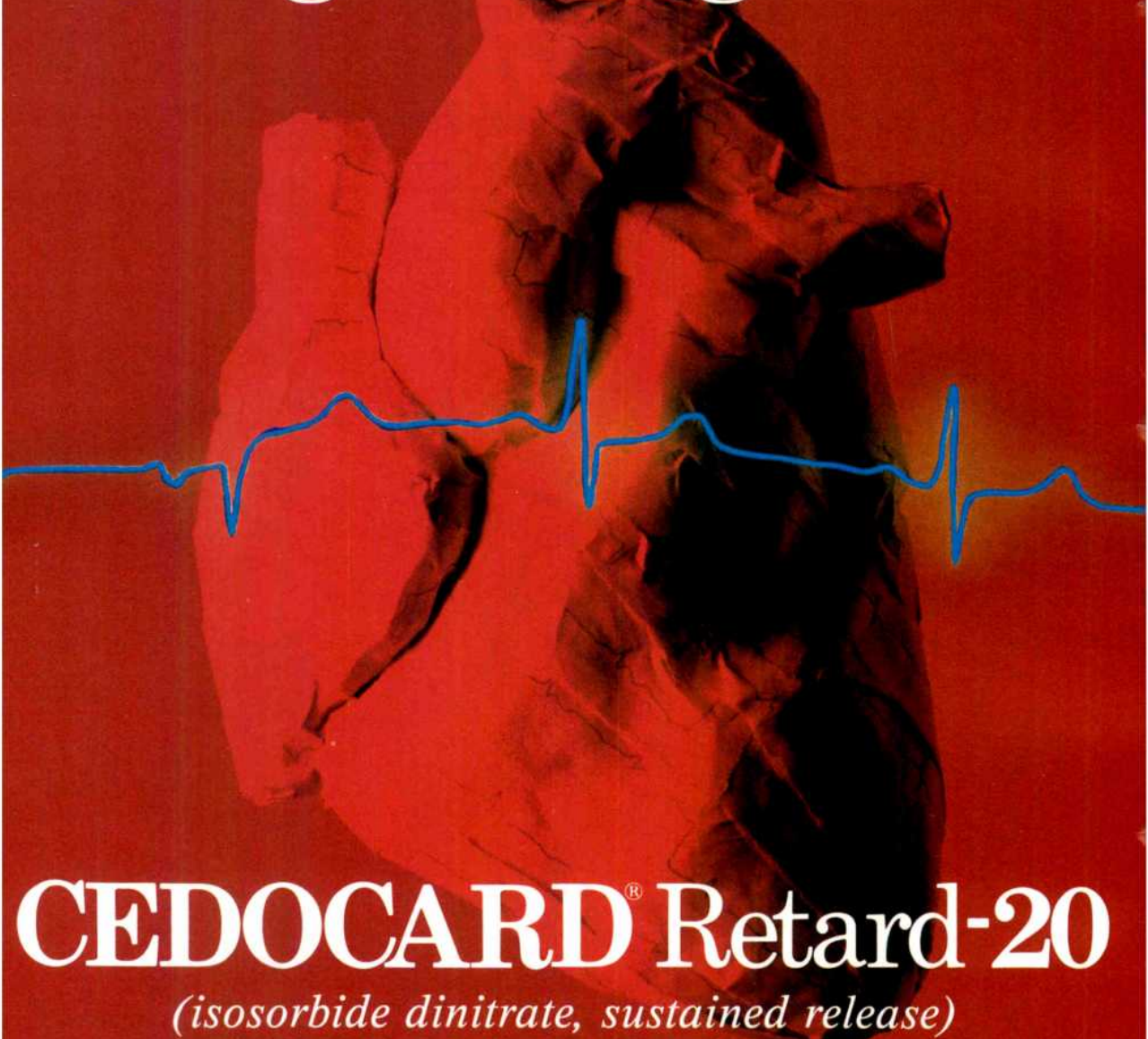
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Syndrome X: the haemodynamic significance of ST segment depression

RICHARD D LEVY, LEONARD M SHAPIRO, CHRISTINE WRIGHT,
LORNA MOCKUS, KIM M FOX

From the National Heart Hospital, London

SUMMARY The relation between chest pain, ST segment depression, and changes in left ventricular function was assessed in six patients with angina, a positive exercise test, and normal coronary arteries as assessed by arteriography (syndrome X). In the six patients with syndrome X and in six controls there was no significant rise in pulmonary artery diastolic pressure during treadmill exercise, although there was ST segment depression (range 1-4.5 mm) in the patients with syndrome X. In 19 patients with coronary artery disease, however, the pulmonary artery diastolic pressure increased by a median 5 mm Hg (range 0-13.6 mm Hg) on treadmill exercise. In only one patient with coronary artery disease, who showed 1 mm ST segment depression, was there no rise in pulmonary artery diastolic pressure. During ambulatory monitoring in patients with syndrome X there were 12 episodes of ST segment depression (> 1 mm) (4 painful, 8 painless) in which there was no change in pulmonary artery diastolic pressure. In the patients with coronary artery disease there were 29 episodes of angina during ambulatory monitoring and during all of them pulmonary artery diastolic pressure rose by a median 7.5 mm Hg (range 1.8-19.7 mm Hg).

Unlike the haemodynamic changes that usually occur during myocardial ischaemia in coronary artery disease, chest pain and ST segment changes in patients with syndrome X are not associated with impaired left ventricular function as assessed by ambulatory pulmonary artery pressure monitoring.

Syndrome X is defined as anginal chest pain with ST segment depression on exercise and normal coronary arteriography without vascular spasm. The pathophysiological basis of syndrome X has often been studied but remains poorly understood.¹⁻³ We have used ambulatory pulmonary artery diastolic pressure monitoring, which reflects left ventricular end diastolic pressure,^{4,5} to investigate the haemodynamic changes accompanying ST segment depression during treadmill exercise and unrestricted ambulatory activity in patients with syndrome X and we have compared these results with those in patients with coronary artery disease.

Patients and methods

PATIENTS

We studied three groups of patients (a) six with syndrome X (5 male, 1 female, mean (SD) age 48 (12) years) all of whom had had negative responses to ergometrine maleate provocation and no evidence of ST segment elevation on 24 hour ambulatory electrocardiographic monitoring; (b) six controls (4 male, 2 female, mean age 39 (7) years) with chest pain of non-cardiac origin, normal exercise test, and normal coronary arteriography; (c) 19 men (mean age 57 (11) years) with coronary artery disease (anginal chest pain with positive exercise test and $> 50\%$ narrowing in one or more coronary arteries).

All antianginal medication other than glyceryl trinitrate was discontinued 48 hours before the study. The protocol was approved by the hospital ethics committee and patients gave their informed and written consent.

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PULMONARY ARTERY PRESSURE MONITORING

A polyurethane six French NIH type catheter with a miniature strain gauge transducer mounted on the tip was immersed in saline for an hour before use and was calibrated. The transducer was driven and demodulated by an electrically isolated Gaeltec pre-amplifier. The catheter was introduced percutaneously via a subclavian vein to a proximal pulmonary artery under fluoroscopy in the cardiac catheter laboratory when the patient was undergoing cardiac catheterisation. The pulmonary artery pressure was recorded on an Oxford Medilog I miniature tape recorder that had been modified by the insertion of an AM4 pressure module.⁴

ST SEGMENT MONITORING

ST segment monitoring was performed with a frequency modulated recorder and leads CM2 and CM5 were recorded. The electrocardiogram was replayed on an Oxford MA20 scanner. Changes in the ST segment were measured 80 ms after the J point to an accuracy of 0.1 mm by means of a magnifying lens equipped with a graticule. A change of 1 mm ST segment depression lasting more than 30 seconds was regarded as significant. The heart rate and ST segment changes were analysed on a beat to beat basis for 5 min before each episode and again up to 5 min after the ST segment had returned to basal levels.

The pulmonary artery pressure recording was linked to the frequency modulated electrocardiogram by an event button that when it was pressed marked both the frequency modulated electrocardiogram and the pulmonary artery trace. Ambulatory pulmonary artery pressure monitoring and ST segment monitoring were performed for 24–48 hours in each patient.

EXERCISE TESTING

Exercise testing was performed according to a modified Bruce protocol.⁶ Transducer tipped pulmonary artery pressure and the frequency modulated electrocardiogram were recorded continuously. A 12 lead electrocardiogram was recorded at one minute intervals. The exercise test was terminated by anginal pain, dyspnoea, multiple ventricular extrasystoles, hypotension, ST segment depression

> 3 mm, or exhaustion.

ANGINA DIARY

Patients were instructed to keep diaries during the period of ambulatory pulmonary artery pressure and ST segment monitoring. They were asked to note the time of onset and severity of chest discomfort and their activity at the time of pain. In addition, they were asked to press the event marker so that both the ST segment and pulmonary artery traces were marked.

At the end of 24–48 hours of recording, the pulmonary artery catheter was removed and the pulmonary artery trace was replayed through a PB2 and PM3 unit. This was displayed on an oscillograph (SE Laboratories 6008). The entire period of recording of the pulmonary artery diastolic pressure was displayed on ultraviolet paper and measured by means of a calibrated scale from a zero reference point. The pulmonary artery diastolic pressure was measured during both painful and painless episodes of ST segment depression on a beat to beat basis 5 min before the onset of the earliest change in pulmonary artery pressure and for 5 min after the pulmonary artery pressure had returned to baseline values. The pulmonary artery diastolic pressure was measured at the end of expiration in each respiratory cycle.

STATISTICAL ANALYSIS

A significant change in the basal ST segment, heart rate, or pulmonary artery diastolic pressure was taken to be a change of at least 3 SD from a mean level measured over 5 min before any change in the pulmonary artery pressure or ST segment. Wilcoxon rank sum testing was used for analysis.

Results

EXERCISE TESTING

In patients with syndrome X and normal controls there was no important increase in pulmonary artery diastolic pressure during treadmill exercise despite the development of ST segment depression in those with syndrome X (table 1). Five of the six control patients reached stage 4 with a heart rate > 150 beats/min. In one control patient pulmonary artery

Table 1 *Changes in the ST segment and pulmonary artery diastolic pressure during treadmill exercise in patients with syndrome X, coronary artery disease, and in controls*

	Syndrome X	Coronary artery disease	Controls
ST segment change (mm)	1.7 (1.4–5)*	1.9 (1.5–2)*	0 (0)
Increase in pulmonary artery diastolic pressure: mm Hg	0 (0–4.4)	5 (0–13.8)	0 (0–3)
0.0	0 (0–72)†	69 (0–262)‡	0 (0–55)‡

Medians and ranges are shown.

*NS; †, ‡, $p < 0.01$.

diastolic pressure rose by 2 mm Hg and in another by 3 mm Hg on exercise in the absence of electrocardiographic changes. There was no change in pulmonary artery diastolic pressure in the remaining control subjects.

Pulmonary artery diastolic pressure did not rise in four of the six patients with syndrome X (fig 1); in the remaining two patients it rose by 3 and 4.4 mm Hg. All patients reached at least stage 3 of the modified Bruce protocol (median 11.9 min, range 7.4–17) and had an increase in heart rate (median 155, range 135–190 beats/min). All the patients with syndrome X had ST segment depression (median 1.7 mm, range 1–4.5).

Changes on treadmill exercise in patients with coronary artery disease are included for comparison (table 1, fig 2). The results have been reported previously.⁷ In most patients with coronary artery disease there was a significant rise in pulmonary artery diastolic pressure associated with ST segment depression and angina.

AMBULATORY MONITORING

Twelve episodes of ST segment depression > 1 mm (4 painful and 8 painless) were recorded in patients

with syndrome X (table 2). All episodes occurred between 6 am and 9 pm. Pulmonary artery diastolic pressure did not rise during these episodes, even when an episode of ST segment depression of 2.2 mm lasted 52 minutes.

In patients with coronary artery disease there were 29 anginal episodes with ST segment depression all of which were associated with a rise in pulmonary artery diastolic pressure (median 87.5%, range 20–237).

Discussion

The pathophysiology of the syndrome of chest pain with a positive exercise test and normal coronary arteriography is poorly understood. We have shown that in patients with syndrome X there were no changes in pulmonary artery diastolic pressure during ambulatory monitoring and treadmill exercise despite chest pain and ST depression. In patients with arteriosclerotic coronary artery disease changes in pulmonary artery diastolic pressure reflected impaired left ventricular function that was seen during myocardial ischaemia.⁷

Ambulatory pulmonary artery pressure moni-

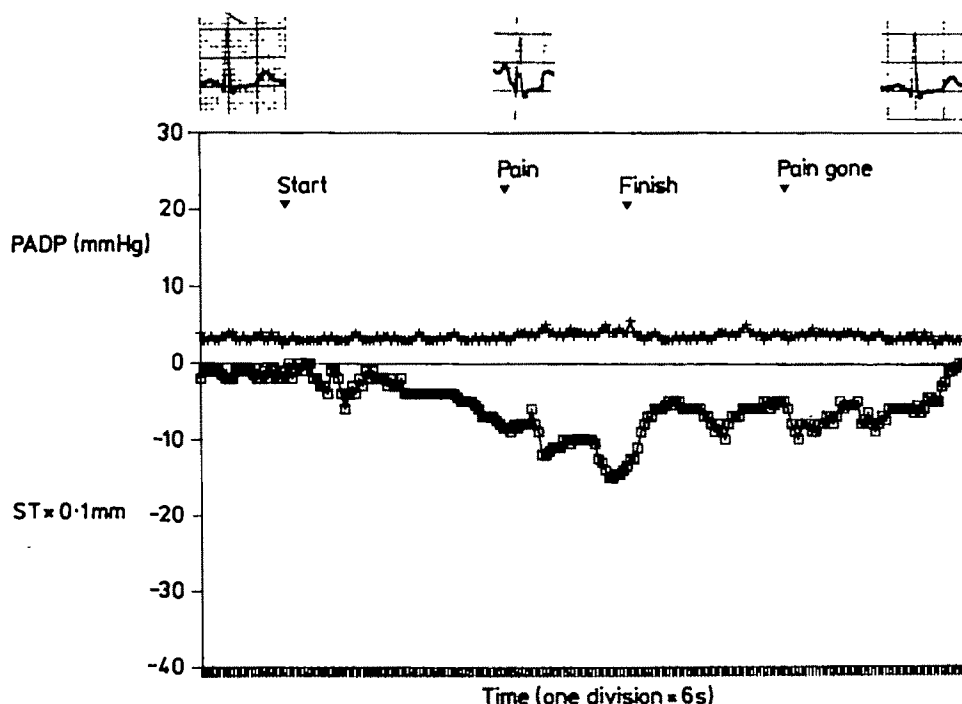


Fig 1 Changes in the ST segment and pulmonary artery diastolic pressure (PADP) during treadmill exercise in a patient with syndrome X. There was no rise in pulmonary artery diastolic pressure despite important ST segment depression. Maximum heart rate was 160 beats/min.

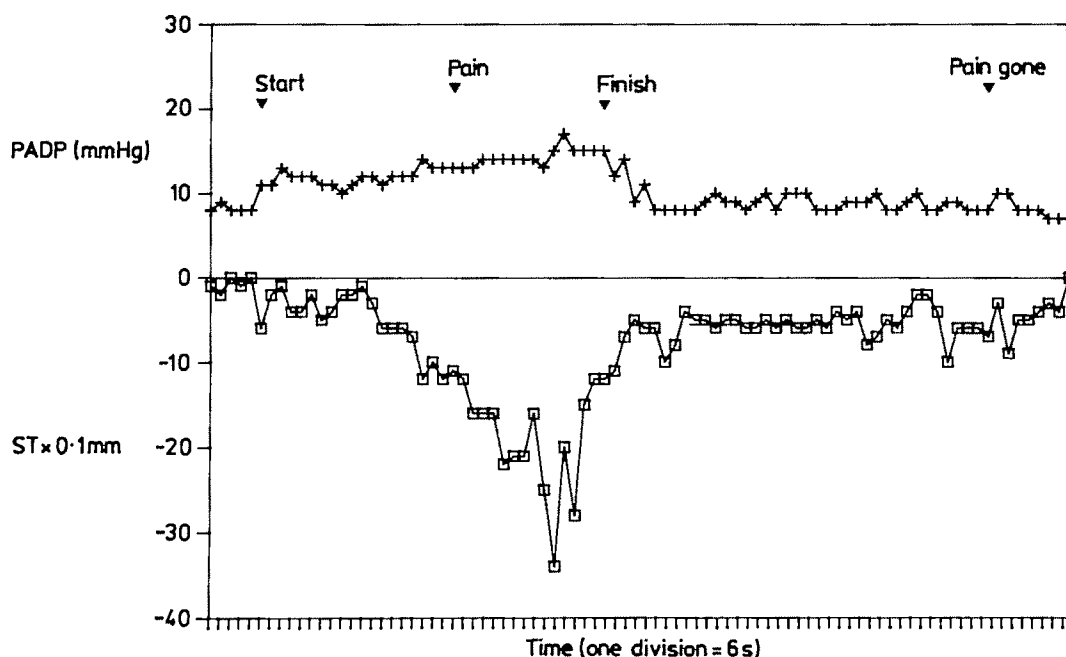


Fig 2 Changes in the ST segment and pulmonary artery diastolic pressure (PADP) during treadmill exercise in a patient with coronary artery disease. There was a rise in pulmonary artery diastolic pressure with significant ST segment depression. Maximum heart rate was 130 beats/min.

Table 2 Changes in the ST segment and pulmonary artery diastolic pressure during ambulatory monitoring in syndrome X and coronary artery disease

	Syndrome X	Coronary artery disease
Number of episodes	12	29
ST segment change (mm)	1.35 (1-3)	1.5 (1-4)
Increase in pulmonary artery diastolic pressure.		
mm Hg	0 (0-1)	7.5 (1.8-19.7)
%	0 (0-15)*	87.5 (20-237)*

Medians and ranges are shown

* $p < 0.001$

toring with a transducer tipped catheter has been shown to be a reliable method of assessing pulmonary artery diastolic pressure in ambulant patients.⁴ Beat to beat analysis of the ST segment and pulmonary artery diastolic pressure during periods of interest can be performed and the drawbacks of fluid filled systems have been overcome.

There have been many studies of syndrome X, often with conflicting results. One of the difficulties has been that there are no uniform diagnostic criteria.^{1,8} Patients without a positive exercise test have been included in some studies.^{9,10} All patients in our

study had a positive exercise test. In addition, coronary arteriography was performed in multiple views to reduce the possibility of inadequate opacification and misinterpretation of the coronary arteriograms.

Several explanations have been suggested for the mechanism of syndrome X. An early concept was that it was a disease of the small vessels¹¹; however, biopsy specimens showed no evidence of this,^{2,10} though vessels between 40 and 200 μ m cannot be seen adequately by light or electron microscopy or by angiography.² It has been suggested that coronary dilatory capacity is considerably reduced in syndrome X,^{2,12,13} as it is in atherosclerotic coronary artery disease, and that vasoconstrictor stimuli such as the cold pressor test or ergometrine maleate provocation may unmask the flow abnormality.^{3,14} This may be caused by abnormal arteriolar regulation of calcium handling¹⁵ and certainly calcium antagonists prolong exercise duration and the time to the onset of ST segment depression in some though not all patients with syndrome X.¹⁶

Some patients with syndrome X have abnormal myocardial lactate production, and mitochondrial abnormalities have been seen by electron microscopy.² Regional perfusional abnormalities were identified in some patients by xenon-133 imaging, and this accords with the concept of a compromised

flow disorder.¹⁷ Gated blood pool studies have also shown abnormal left ventricular function in response to isometric stress.^{2,3}

We found that if there is an alteration in coronary blood flow in syndrome X it is insufficient to cause a rise in left ventricular filling pressure, as it does in patients with proven coronary artery disease. Furthermore, because the prognosis for patients with syndrome X is good^{1,18} it is likely that the abnormality is of little haemodynamic importance.

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Exercise capacity and spontaneous heart rhythm after transvenous fulguration of atrioventricular conduction

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SUMMARY Twenty nine patients who had had refractory supraventricular tachycardia were studied 4-36 (mean 16) months after transvenous fulguration of the atrioventricular junction. Twenty two had complete atrioventricular block, five partial atrioventricular block, and two had atrioventricular conduction via an accessory atrioventricular pathway. Though all patients were free of palpitation after the procedure, exertional dyspnoea had developed in 13 and in two patients pre-existing dyspnoea had worsened. During ventricular demand pacing, exercise time was reduced to 43% of the predicted value for their age and sex. The 16 patients with rate responsive pacemakers demonstrated a significantly better but still impaired exercise capacity during "physiological" pacing as compared with their performance during constant rate pacing. In patients with complete atrioventricular block there was an increase in spontaneous ventricular rate during exercise in seven patients and in response to the Valsalva manoeuvre in eight patients. This suggests that the intrinsic ventricular pacemaker is influenced by autonomic nervous system activity in some patients.

It is concluded that though transvenous fulguration is successful in controlling tachycardia it may reduce exercise capacity. Most patients remain in complete atrioventricular block after the procedure and, in contrast with the practice as described in early reports, would benefit from "physiological" pacing—though even with this mode exercise capacity is likely to be abnormal.

Transvenous fulguration of atrioventricular conduction is a new technique used to treat recurrent supraventricular tachycardia in patients who do not respond adequately to, or who cannot tolerate, drug treatment and in whom antitachycardia pacing, where applicable, has proved ineffective.¹⁻³ Little is known about its long term sequelae, though earlier reports have documented the rhythms produced.⁴ This study was prompted by the frequent complaints of breathlessness and reduced exercise tolerance from patients after transvenous fulguration of atrioventricular conduction. The aims were to assess exercise capacity and spontaneous heart rhythm, including response to exercise and the Valsalva manoeuvre, after atrioventricular fulguration.

Patients and methods

We studied 29 patients (aged 19-67, 22 female). All patients had had frequent symptomatic supraventricular tachycardia and were refractory to or intolerant of antiarrhythmic drugs. Three patients had previously had antitachycardia pacemakers implanted that had not been consistently effective in controlling their symptoms. The arrhythmia that they had was atrioventricular reentrant tachycardia in eight patients, atrioventricular nodal reentrant tachycardia in eight, paroxysmal atrial fibrillation in seven (three had mitral valve disease), paroxysmal atrial tachycardia in two (one had mitral valve disease), and chronic atrial fibrillation/flutter in four (three had mitral valve disease). Though seven patients had mitral valve disease, the remaining 22 patients had no evidence of structural heart disease before transvenous atrioventricular fulguration.

Except for one patient transvenous atrioventricular fulguration was performed under general

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anaesthesia by the technique described previously.⁴ In each case, 1–3 DC shocks of 200–400 J (stored) were delivered to the pole producing the largest unipolar His deflection and a clearly defined atrial electrogram. All patients subsequently had a permanent pacemaker implanted.

For this study, patients were admitted to hospital to assess exercise capacity and spontaneous heart rhythm from 4 to 36 (mean 16) months after transvenous fulguration. The patients were fitted with a Holter cassette recording system after admission. In all cases, during ventricular demand pacing the ventricular rate was gradually reduced to the lowest that the patient could comfortably tolerate, but not <30 beats/min. In those patients who did not demonstrate a spontaneous heart rhythm the implanted pacemaker was briefly inhibited to determine the escape interval. The patients rested in bed during their admission (usually for about eight hours) with the pacemaker programmed to a low rate to assess any change in spontaneous heart rhythm. The patients performed the Valsalva manoeuvre during

continuous electrocardiographic monitoring so that we could assess the response of the spontaneous heart rhythm to changes in autonomic nervous system activity.

Patients' pacemakers were then temporarily programmed to ventricular demand mode at 60 or 70 beats/min for exercise testing. Twenty eight patients performed symptom-limited treadmill exercise testing according to the standard Bruce protocol to assess exercise capacity and the response of the spontaneous heart rhythm to exercise. The remaining patient, who had mitral valve disease, was considered unsuitable for exercise testing because of her poor exercise tolerance. Sixteen patients with "physiological" pacing systems (10 with P wave synchronised and six with TX (ventricular, QT sensing, rate-responsive) systems) who had been in "physiological" mode since the time of fulguration were exercised in a randomised double-blind manner in ventricular demand mode and rate responsive mode, with at least a 30 min recovery period in between. We analysed group differences by a one way analysis of

Table 1 Clinical details and spontaneous heart rhythm of 29 patients after transvenous fulguration of atrioventricular conduction

Case No	Age (yr)	Sex	Primary arrhythmia	No of fulguration sessions	Time since fulguration (month)	Spontaneous heart rhythm	R-R interval (ms) during spontaneous rhythm	Type of pacemaker
1	26	F	AVRT	1	34	S/R 1°HB	NA	VVI
2	46	F	AVRT	1	8	CHB	2420	TX
3	25	F	AVNRT	1	20	CHB	1392	DDD
4	19	F	AVNRT	2	7	CHB	1450	DDD
5	39	F	AVNRT	1	19	CHB	1340	DDD
6	58	F	PAF	1	20	CHB	1940	TX
7	37	F	PAT	1	36	S/R 1°HB	NA	VVI
8	46	M	AVRT	1	18	S/R†	NA	VVI
9	51	F	PAF	1	19	CHB	> 5140	TX
10	33	F	AVRT	1	7	CHB	1310	DDD
11	32	F	AVRT	1	20	CHB	> 6720	VVI
12	57	F	AVNRT	1	13	CHB	1340	DDD
13	47	F	AVRT	1	16	CHB	1320	DDD
14	52	F	AVNRT	1	23	CHB	1660	DDD
15	20	M	AVRT	1	25	S/R†	NA	VVI
16*	66	F	PAF	1	7	CHB	2480	VVI
17	60	F	AVNRT	2	16	S/R 2°HB	NA	DDD
18	32	F	AVNRT	1	31	S/R	NA	DDD
19*	65	F	ChAF	1	13	CHB	> 4840	VVI
20	55	M	PAF	1	15	CHB	1210	VVT
21†	67	M	PAT	2	18	CHB	1300	VVI
22†	61	F	PAF	2	15	CHB	> 4800	VVI
23	63	F	ChAF/ChAFL	1	4	A flutter	NA	TX
24	30	F	AVRT	1	4	CHB	1180	DDD
25	61	M	PAF	1	6	CHB	1480	TX
26*	48	M	PAF	1	4	CHB	1960	TX
27*	60	F	ChAF	1	6	CHB	1460	VVI
28*	63	F	ChAF	1	9	CHB	1600	VVI
29	53	F	AVNRT	1	26	CHB	1140	VAT

*Mitral valve replacement. †Mitral stenosis. ‡Conduction via accessory pathway. A flutter, atrial flutter; AVRT, atrioventricular tachycardia; AVNRT, atrioventricular nodal tachycardia; ChAF, chronic atrial fibrillation; ChAFL, chronic atrial flutter; CHB, complete heart block; DDD, dual chamber pacemaker; NA, not applicable; PAF, paroxysmal atrial fibrillation; PAT, paroxysmal atrial tachycardia; S/R, sinus rhythm; S/R 1°HB, sinus rhythm with first degree heart block; S/R 2°HB, sinus rhythm with second degree heart block; TX, ventricular, QT sensing pacemaker; VAT, ventricular paced, atrial sensed pacemaker; VVI/VVT, ventricular demand pacemaker.

variance and by a two way analysis of variance for repeated measures on one factor (mode of pacing). We compared proportions by the χ^2 test.

Results

SPONTANEOUS HEART RHYTHM

Table 1 shows the clinical details and spontaneous heart rhythm at the time of this study. Twenty two patients had complete atrioventricular block, four had sinus rhythm (conducted with first degree atrioventricular block in two and with second degree block in one), two had 1:1 atrioventricular conduction maintained via an accessory atrioventricular pathway, and one had atrial flutter with 5:1 atrioventricular conduction.

Immediately after fulguration all patients had remained in complete atrioventricular block for at least 24 hours, apart from patient 8 in whom conduction was maintained via a bundle of Kent. Subsequently, four patients had required repeat fulguration because of a return of atrioventricular conduction, which had occurred within the first week in three. Of the five patients who had evidence of atrioventricular conduction at the time of this study, conduction had returned within the first month in only two. Atrioventricular conduction did not return in any patient 6 months after fulguration. Although patient 21 developed first degree atrioventricular block two days after the procedure, during atrial tachycardia 2:1 atrioventricular conduction was present. After six months, however, 1:1 atrioventricular conduction was present during atrial tachycardia and repeat fulguration was necessary.

Accessory pathway conduction had been present since fulguration in one patient in whom atrio-

ventricular conduction was maintained via an accessory atrioventricular pathway. In the other patient, who was in paced rhythm immediately after fulguration, accessory pathway conduction became apparent for the first time during the second month after the procedure.

It was not possible to assess conduction via the normal atrioventricular pathway from the surface electrocardiogram in the two patients with accessory pathway conduction, but, of the remaining 27, five had evidence of atrioventricular conduction (group 1), 11 had complete atrioventricular block with a spontaneous ventricular rate ≥ 40 beats/min (group 2), and 11 had complete atrioventricular block with a ventricular rate < 40 beats/min (group 3). The ratio of low right atrial to His bundle electrograms (A:H ratio) immediately before fulguration was greatest in group 1 and least in group 3; these differences did not reach statistical significance. In addition, there was no significant difference in the HV interval (time from His bundle electrogram to onset of ventricular depolarisation) before fulguration between the three groups.

Table 2 shows the response of spontaneous heart rhythm to exercise. During exercise seven patients with complete atrioventricular block demonstrated an increase in intrinsic ventricular rate. The patient with atrial flutter showed enhancement of atrioventricular conduction on exercise, whereas two patients with first degree atrioventricular block before exercise developed an increase in the degree of block. One of the patients with accessory pathway conduction demonstrated rate dependent accessory pathway block on exercise.

Table 3 shows the response of spontaneous heart rhythm to the Valsalva manoeuvre. Eight patients

Table 2 Spontaneous heart rhythm and its response to exercise in 28 patients after transvenous fulguration of atrioventricular conduction

		<i>Before exercise</i>		<i>During exercise</i>	
<i>Spontaneous heart rhythm</i>		<i>Rhythm</i>	<i>Ventricular rate (beats/min)</i>	<i>Rhythm</i>	<i>Ventricular rate (beats/min)</i>
CHB (n = 21):	3	VVI pacing	70	VVI pacing	70
	11	VVI pacing	60	VVI pacing	60
	5	VVI pacing	60	CHB	Mean 77
	2	CHB	Mean 48	CHB	Mean 58
Patients with A/V conduction (n = 5):	1	S/R	75	S/R	143
	1	S/R 1° HB	74	2:1 A/V block	77
	1	S/R 1° HB	60	CHB	75
	1	3:2 Wenckebach	Mean 84	3:2 Wenckebach	Mean 120
	1	A flutter, 5:1 A/V block	60	A flutter, 3:1 A/V block	100
S/R with AP conduction (n = 2):	1	S/R	79	S/R	158
	1	S/R	71	2:1 A/V block	100

See footnote to table 1. AP, accessory pathway; A/V, atrioventricular.

Table 3 Spontaneous heart rhythm and its response to the Valsalva manoeuvre in 29 patients after transvenous fulguration of atrioventricular conduction

Spontaneous heart rhythm		Before Valsalva manoeuvre		During Valsalva manoeuvre	
		Rhythm	Ventricular rate (beats/min)	Rhythm	Ventricular rate (beats/min)
CHB (n = 22).	1	VVI pacing	70	VVI pacing	70
	1	VVI pacing	60	VVI pacing	60
	6	VVI pacing	≤ 50	VVI pacing	≤ 50
	1	VVI pacing	50	CHB	53
	7*	CHB	Mean 44	CHB	Mean 48
	6†	CHB	Mean 41	CHB	Mean 42
Patients with A/V conduction (n = 5):	1	S/R	80	S/R	100
	1	S/R 1° HB	60	S/R 1° HB	75
	1	S/R 1° HB	65	2:1 A/V block	85
	1	3:2 Wenckebach	Mean 84	2:1 A/V block	71
	1	A flutter 5/6:1 A/V block	Mean 55	A flutter 4:1 A/V block	75
S/R with AP conduction (n = 2).	1	S/R	83	S/R	111
	1	S/R	71	2:1 A/V block	51

*Seven patients in whom R-R interval decreased by > 40 ms in response to Valsalva manoeuvre.

†Six patients in whom R-R interval decreased by ≤ 40 ms in response to Valsalva manoeuvre.

See footnotes to tables 1 and 2

with complete atrioventricular block demonstrated an increase in spontaneous ventricular rate (R-R interval decreased by > 40 ms) in response to the Valsalva manoeuvre. In a further six patients the R-R interval did not decrease by > 40 ms and in this group the intrinsic ventricular rate before Valsalva was lower. Two patients developed a rate dependent increase in atrioventricular block, as did one patient with accessory pathway conduction, in response to Valsalva. The patient with atrial flutter demonstrated enhanced atrioventricular conduction.

During Holter monitoring at rest, with the pacemaker programmed to a low rate ventricular demand mode, seven patients demonstrated a variation in the degree of atrioventricular block, including one patient who showed both first degree and complete atrioventricular block.

EXERCISE CAPACITY

The 28 patients exercised during ventricular demand pacing at 60 or 70 beats/min demonstrated a decreased exercise capacity. Mean (SD) exercise time was 43 (24)% of the predicted value for their age and sex.⁵ The six patients with mitral valve disease had a lower exercise capacity (37 (25)%) than those without evidence of structural heart disease (45 (24)%), though the difference was not statistically significant. The reason for termination of exercise was dyspnoea in 19 patients; dyspnoea and dizziness in three; dyspnoea and fatigue in three; and dizziness, fatigue, or intermittent claudication in the remainder. The 16 patients with rate responsive pacemakers demonstrated a significantly better but still impaired exercise capacity during "physiological" pacing (63 (25)%) compared with their performance during constant rate pacing (37 (19)%) ($p < 0.001$) (fig 1). There was no correlation between

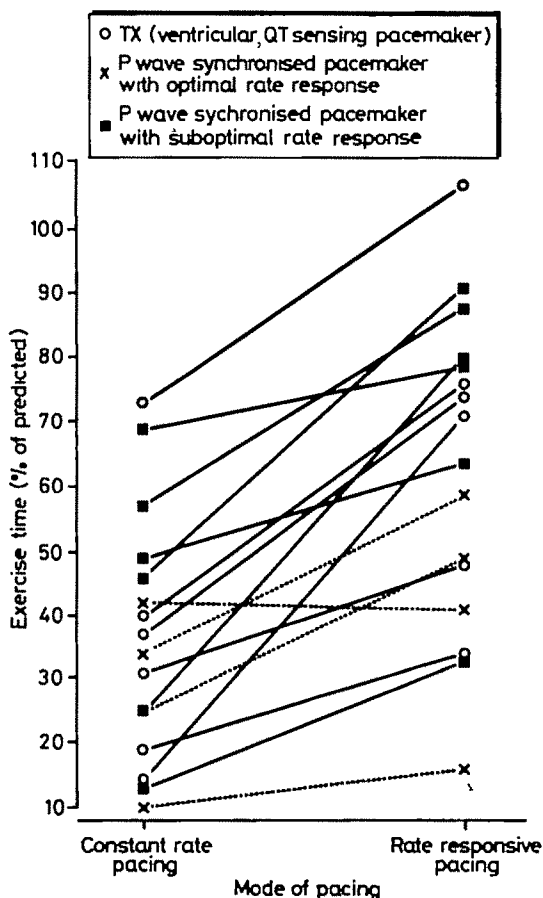


Fig 1 Exercise time (as % of predicted) during constant rate and rate responsive pacing in 16 patients with "physiological" pacing systems.

Table 4 Exercise capacity (mean (SD)) in constant rate ventricular demand and rate responsive modes in 16 patients with "physiological" pacing systems

	Exercise capacity (% of predicted) during VVI pacing	Exercise capacity (% of predicted) during rate responsive pacing
TX pacemaker (n = 6)	35.7 (20.9)	68.3 (25.2)
DDD with optimal rate response (n = 4)	27.8 (13.7)	41.4 (18.4)
DDD/VAT with suboptimal rate response (n = 6)	43.2 (20.7)	72.5 (21.5)

See footnote to table 1.

exercise capacity during constant rate or "physiological" pacing and the mean (SD) maximum rise in any of three enzymes (creatinine kinase 658 (793) IU/l, lactate dehydrogenase 777 (689) IU/l, and aspartate transaminase 115 (196) IU/l) after atrioventricular fulguration.

During exercise testing the six patients with TX (ventricular, QT sensing) pacemakers demonstrated an adequate rate response, the mean (SD) R-R interval decreasing from 823 (8) ms before exercise to 488 (70) ms at maximum exercise. Four of the 10 patients with dual chamber pacemaker systems showed an appropriate increase in ventricular rate during exercise (optimal rate response). The remaining six, however, reached the maximum ventricular rate response to sensed atrial activity before the point of termination of exercise and consequently the ventricular rate fell abruptly (suboptimal rate response). This fall in the ventricular rate is related to pacemaker blocking modes. Table 4 shows the exercise capacity of these 16 patients in constant rate ventricular demand and rate responsive modes. There was no significant difference in the degree of improvement during "physiological" pacing as compared with constant rate pacing between the three

groups. Therefore, a suboptimal rate response did not appear to produce less improvement in exercise capacity during "physiological" pacing.

The most striking feature in these patients at review after transvenous atrioventricular fulguration was the frequency of exertional dyspnoea. Although all patients had been free of palpitation after the procedure, 13 patients had developed exertional dyspnoea and in two patients pre-existing dyspnoea has worsened. Two patients with mitral valve replacement and chronic atrial fibrillation who had had a rapid ventricular response (cases 27 and 28) had become less dyspnoeic after the procedure (table 5). Before atrioventricular fulguration none of the 22 patients without evidence of structural heart disease complained of exertional dyspnoea. Although 13 complained of breathlessness after the procedure, this was not related to the type of pacemaker implanted; of those who complained of exertional dyspnoea, four had constant rate and nine had rate responsive pacemakers, and of those who remained free of dyspnoea, three had constant rate and six had rate responsive pacemakers. Eleven patients who complained of exertional dyspnoea and four who did not had complete atrioventricular block at the time of this study (table 5).

The patients with exertional dyspnoea had a significantly shorter exercise time ($p < 0.01$) than the nine who remained symptom free when exercised in their usual pacing mode (fig 2). Only four patients had exercise tests before undergoing transvenous atrioventricular fulguration. In these patients exercise capacity during treadmill testing before and after fulguration corresponded with the presence or absence of exertional dyspnoea.

Discussion

Most patients with recurrent supraventricular tachycardia respond satisfactorily to antiarrhythmic drug treatment. Surgical intervention, for example localised atrial excision^{6,7} and ablation of an accessory pathway,^{8,9} has been used for a few patients who

Table 5 Presence of exertional dyspnoea before and after the procedure in 29 patients undergoing transvenous fulguration of atrioventricular conduction

Exertional dyspnoea before fulguration	Exertional dyspnoea after fulguration	No of patients	Spontaneous heart rhythm		
			CHB	A/V conduction	AP conduction
No	No	9	4	3	2
No	Yes	13	11	2	0
Yes	Yes (same)	3*	3	0	0
Yes	Yes (worse)	2†	2	0	0
Yes	Yes (better)	2*	2	0	0

*Mitral valve replacement. †Mitral stenosis. See footnotes to tables 1 and 2.

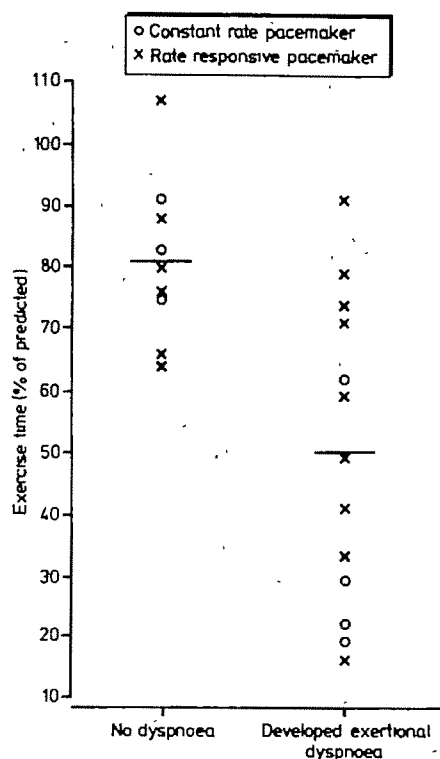


Fig 2 Exercise time (as % of predicted) after atrioventricular fulguration of 22 patients without structural heart disease. Mean values are shown for the 13 who developed exertional dyspnoea and the nine who did not.

were refractory to or intolerant of such treatment. For most patients, however, the only surgical treatment that is appropriate is ablation of the atrioventricular node and His bundle.^{10 11} Catheter techniques for producing atrioventricular block avoid open heart surgery.¹⁻³ Although the technique has been reported to be safe and effective⁴ little has been reported about the long term results.

At follow up an average of 16 months after fulguration, 76% of patients in the current series had complete atrioventricular block. Similar results were reported in an earlier study⁴ (74%) and also after cryosurgical ablation of the atrioventricular node and His bundle (77%).¹² Repeat fulguration was necessary in 14% of patients because atrioventricular conduction had returned, usually within the first few days. In 10% of patients undergoing fulguration, however, atrioventricular conduction returned more than four weeks after the procedure, but there was no recovery of conduction after six months.

Gallagher *et al* have suggested that the best results are obtained by ablating the proximal portion of the His bundle,¹ which is identified by recording the longest possible HV interval associated with a large His bundle deflection and an atrial electrocardiogram > 0.25 mV. The HV interval immediately before fulguration in our series did not predict the long term result, and although patients with complete atrioventricular block and a low ventricular rate had the smallest A:H ratio, the number of patients was too small to draw a definite conclusion. Persistent complete atrioventricular block is not essential for tachycardia control.

Our results suggest that the intrinsic ventricular pacemaker is influenced by autonomic nervous system activity in some patients. Of the patients with complete atrioventricular block, 33% demonstrated a reduction in cycle length of the intrinsic ventricular pacemaker with exercise and 36% in response to the Valsalva manoeuvre. The intravenous administration of atropine in previous studies was found to have no effect on the rate of the intrinsic ventricular pacemaker^{2 12} and the implanted pacemaker was not inhibited by spontaneous ventricular activity during treadmill exercise testing,^{2 12} although only a few patients were studied. Klein *et al* showed that an isoprenaline infusion significantly increased the rate of the intrinsic ventricular pacemaker in a dose related manner after cryosurgical ablation of atrioventricular conduction.¹² The mean cycle length of the spontaneous ventricular rhythm in our patients was 1555 ms (range 1140–2480 ms), which resembles that reported for patients with intra-hisian block secondary to disease of the conduction system.^{13 14} In some patients with persistent atrioventricular conduction there was a rate dependent increase in the degree of atrioventricular block in response to exercise and the Valsalva manoeuvre. The degree of atrioventricular block also varied in individual patients during several hours of rest, which implies that the spontaneous heart rhythm or escape interval observed at routine pacemaker clinic visits may not accurately reflect the state of the atrioventricular conducting system.

We were concerned that over 50% of our patients had developed exertional dyspnoea or had had worsening of pre-existing dyspnoea after atrioventricular fulguration. Exercise capacity during ventricular demand pacing was reduced to 43% of the predicted value for their age and sex. The 16 patients with rate responsive pacemakers demonstrated a significantly better but still impaired exercise capacity during "physiological" pacing as compared with their performance during constant rate pacing. Not all the patients in our study had an exercise test before fulguration. Increases in cardiac enzymes have been

reported after catheter induced atrioventricular fulguration,^{12,4} although there was no other evidence of myocardial damage or important long term complications. Atrioventricular fulguration with an active fixation electrode and low energy shocks (50 J) has been attempted,¹⁵ but this also produced similar changes in creatine kinase concentrations. The cause of the impaired exercise capacity and exertional dyspnoea in our patients remains uncertain but possibilities include the presence of or progression of coexisting heart disease, the implantation of constant rate pacemakers, pacemaker malfunction, myocardial or valvar damage produced at the time of fulguration, and impairment of the sinus node response to physiological stimuli.

During constant rate ventricular pacing the exercise capacity of patients without evidence of structural heart disease was reduced to 45% of that predicted. Most of these patients had reentrant tachycardia and almost certainly will have had otherwise normal hearts before atrioventricular fulguration. Atrial synchronised ventricular pacing improves exercise performance in most patients in complete heart block more than constant rate ventricular pacing.^{16,17} This improved work capacity is largely the result of the chronotropic response to exercise rather than the maintenance of the normal sequence of cardiac chamber activation.^{18,19} Although 41% of our patients had constant rate ventricular demand pacemakers, the exercise time of those with rate responsive systems was reduced to 63% of that predicted during "physiological" pacing. We also found that the development of exertional dyspnoea after atrioventricular fulguration was not related to the type of pacemaker (constant rate or rate responsive) implanted. The group of patients with dual chamber pacing systems who demonstrated a suboptimal rate response during exercise had as impressive an improvement in exercise capacity during "physiological" pacing as patients with optimal dual chamber function and with appropriate TX function. In addition, we found no evidence of sinus node dysfunction in patients with dual chamber systems. It is therefore difficult to attribute the impaired exercise capacity in our patients to coexisting heart disease or limitations of pacemaker function. One possible explanation is that transvenous atrioventricular fulguration impairs right or left ventricular function or both. Surawicz suggested that the lesion produced by atrioventricular fulguration could be appropriately characterised as the equivalent of a small septal infarction²⁰ and it seems likely that there is more extensive damage than a mere interruption of the His bundle.

The results of our study suggest that rate

responsive rather than constant rate pacemakers should be implanted after atrioventricular fulguration, in contrast with the practice described in an early report.² Even with "physiological" pacing, however, exercise capacity is likely to be impaired. Therefore, we believe that young patients with atrioventricular or atrioventricular nodal reentrant tachycardia should only be treated with transvenous atrioventricular fulguration when frequent distressing symptoms persist despite medical treatment and, where appropriate, antitachycardia pacing.

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Ventricular pacing improves exercise tolerance in patients with chronic heart block

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SUMMARY Exercise capacity was assessed by means of a simple six minute walking test in a group of 18 patients with heart block whose only presenting symptom was breathlessness. None was in overt cardiac failure. Patients were studied before and after implantation of a transvenous, ventricular, demand pacing system (study group). Eight patients with an implanted pacemaker admitted for elective generator replacement were assessed in the same manner (control group). Exercise capacity in the study group was significantly increased within 48 hours of pacing, and this improvement was maintained in most patients during the follow up period of up to 30 months. In contrast, exercise capacity was unaffected by generator replacement in the control group.

Simple ventricular pacing produces symptomatic benefit in patients with heart block accompanied by breathlessness. This benefit is apparent within 48 hours of pacing and is maintained; it can be assessed objectively by a six minute walking test.

Indications for implantation of permanent pacing systems in patients with heart block have been termed "hard" (syncope) and "soft" (cerebral dysfunction and cardiac failure). In Britain few pacemakers are implanted for "soft" indications,¹ although recent guidelines from the pacing subcommittee of the joint American College of Cardiology/American Heart Association task force on assessment of cardiovascular procedures include "marked exercise intolerance" as "symptomatic bradycardia" and hence an indication for permanent pacing.² While some patients with heart block and syncope note that their exercise tolerance improves after pacing³ many patients with heart block whose sole complaints are breathlessness or cardiac failure still remain unpaced.⁴ Several studies have shown an improvement in cardiovascular haemodynamic function with pacing at different rates,⁵⁻⁷ but none has related these findings to changes in symptoms. One study concluded that in the absence of syncope pacing was of little symptomatic benefit, but this

was partly based on retrospective review of clinical and radiological data in a group of patients with congestive cardiac failure.³

We have used a simple six minute walking test^{8,9} to assess the effect of ventricular pacing on exercise capacity in a group of patients with heart block whose only presenting symptom was breathlessness.

Patients and methods

Patients with heart block referred to the cardiology department at the Bristol Royal Infirmary from 1 August 1983 to 31 November 1984 were considered for inclusion in the study. All were assessed by history, clinical examination, 12 lead electrocardiogram, and chest radiograph. Patients with regular bradycardia caused by heart block (complete or 2:1) and who suffered from breathlessness without syncope or dizziness were asked to participate. Those with atrial fibrillation and a slow ventricular response, important valvar heart disease, recent myocardial infarction (within three months), overt heart failure (six patients), or heart block after cardiac operation were excluded. Five patients with additional chronic airways disease were included. None had anaemia or hypothyroidism. Drugs likely to interfere with atrioventricular conduction had

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Table 1 Details of patients recruited for the study and results of 6 minute walks

No	Sex	Age	Pre-pace rhythm	Pre-pace rate	Diuretics	T	1	2	3	1 yr	2 yr	Comments
Study group:												
1	M	75	2:1 A-V B	50	None	328	432	486	526(6)	513(18)		Died 19 months
2	M	75	2:1 A-V B	40	Triamterene and hydrochlorothiazide	162	162	297	324(3)		289(29)	Increasing arthritis
3	M	72	CHB	40	Bendroflumazide	351	364	429	486(3)	439(16)		Increasing arthritis, died 20 months
4	F	72	CHB	40	None	459	479	493	486(2)	486(14)		
5	M	64	2:1 A-V B	30	None	364	386	452	472(2)		459(25)	
6	M	77	AF + CHB	42	None	439	418	467	506(1)	502(14)	486(26)	
7	M	77	CHB	40	None	371	351	445	479(1)			Stroke at 9 months; no further walks
8	M	65	CHB	37	None	270	256	351	391(3)			
9	M	65	CHB	40	None	270	270	413	425(1)	461(21)		
10	F	67	2:1 A-V B	40	None	337	391	445	472(1)			Mental illness; no further walks
11	M	79	2:1 A-V B	40	None		189	270	278(6)	236(21)		Increasing COAD
12	F	82	CHB	40	None		286	297	344(8)			
13	M	73	CHB	46	None		359	483	472(3)	486(18)	492(30)	
14	F	53	2:1 A-V B	40	None		418	526	513(1)		490(30)	
15	M	72	CHB	40	None		283	391	378(12)		270(26)	Increasing arthritis
16	M	82	AF + CHB	34	None		324	405	486(1)	337(14)		Increasing arthritis
17	M	90	CHB	40	Bumetanide and potassium chloride		108	216	202(1)		108(14)	Increasing arthritis, died 22 months
18	F	77	2:1 A-V B	30	None		304	367	439(1)			
Patients withdrawn:												
19	M	91†	2:1 A-V B	50	None							
20	M	82*	CHB	46	None							
21	F	67†	AF + CHB	56	Furosemide							
22	F	58†	AF + CHB	40	Furosemide							
23	M	79†	2:1 A-V B	40	None							

2:1 A-V B, 2:1 atrioventricular block; CHB, complete heart block; AF, atrial fibrillation; COAD, chronic obstructive airways disease.

Patients 2, 8, 11, 19, and 21 had chronic airways obstruction. Patient 9 had mild aortic valve regurgitation.

*Patient died before re-study.

†Regained intermittent A-V conduction post-pacing.

T, "training" walk, 1, Immediately before pacing; 2, short term walk at 48 h; 3, long term walk between 1 and 12 months, 1 yr, walk between 13 and 24 months; 2 yr, walk between 25 and 36 months. Walks in metres covered in 6 min. Figure in parentheses indicate months since pacing.

been stopped at least two weeks before pacing but other treatment remained unchanged.

During the study period 268 patients (145 male, 123 female) received a new, permanent pacing system; 172 were judged to be in chronic heart block, while 94 had evidence of intermittent atrioventricular block or sinoatrial disease; two patients had recurrent ventricular tachycardia. Twenty three (13%) patients with "chronic" heart block fulfilled the criteria and were included in the study (table 1). Eighteen patients completed the study and are the subject of this report; five patients were subsequently withdrawn from the study after pacing. All patients were paced by the transvenous route by standard techniques and VVI generators set at 70 beats per minute. Eight patients admitted for elective replacement of a previously implanted pacemaker were used as controls (table 2).

Exercise capacity was assessed by a simple six minute walking test^{8,9} along a hospital corridor (length 27 metres). Subjects were asked to walk as far as they could in six minutes, continuously if possible, but to slow down or to stop for short rests during the test if necessary. The total distance walked was noted as were any stops or symptoms.

To assess any training effect, subjects were exercised twice (if possible) before their procedures (new pacing system or generator change). Subsequent walking tests were performed at 48 hours (the short term test), and again between one and twelve months later (the long term test) when patients returned for their pacing check. In some patients the walking test has been repeated after the one year period (table 1). Each patient was supervised by the same investigator for all of their walking tests.

Results are expressed as mean (1 SD). Student's paired t test was used; statistical significance was taken as $p < 0.05$.

Table 2 Details of control patients

No	Sex	Age	Years paced
24	M	66	4
25	M	61	6
26	M	73	12
27	M	77	4
28	F	78	5
29	F	75	5
30	M	80	5
31	M	79	4

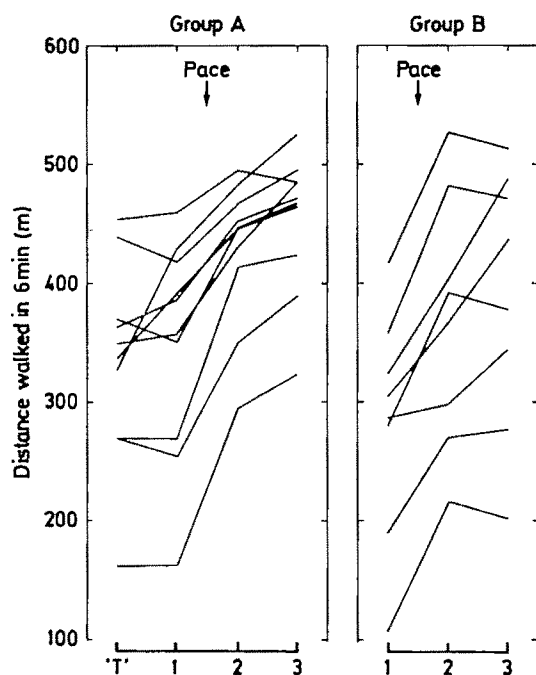


Fig 1 Results of a 6 minute walking test in 10 patients who had two walking tests before pacing (group A) and in eight patients who had one walking test before pacing (group B). T, "Training" walk; (1), immediately before pacing; (2), 48 h after pacing; (3), 1-12 months after pacing. Group A: T vs 1, 334.8 (83.7) vs 348.3 (84.5), NS. Group A + B: 1 vs 2, 318.6 (99.9) vs 399.6 (86.4), $p < 0.001$; 2 vs 3, 399.6 (86.4) vs 423.9 (89.1), $p < 0.05$. All distances are in metres ± 1 SD.

Results

EXERCISE CAPACITY

Group A consisted of 10 patients (eight male, two female; age 64-78, mean (SD) 70.9 (5.2) years) who had two walking tests before pacing. There was no significant difference between the distances walked during these two tests (334.8 (83.7) vs 348.3 (84.5) m), and hence no significant training effect (fig 1).

Group B consisted of eight patients (six male, two female, age 53-90, mean (SD) 76.0 (10.9) years) in whom it was only possible to perform one walking test before pacing (fig 1). There was no significant age or sex difference between groups A and B, which may be regarded as subgroups of the same population, and for further analysis we considered them as one group of 18 patients (13 male, five female, age 53-90, mean 73.1 (8.3) years).

In these 18 patients the distance walked increased from 318.6 (99.9) metres before pacing to 399.6

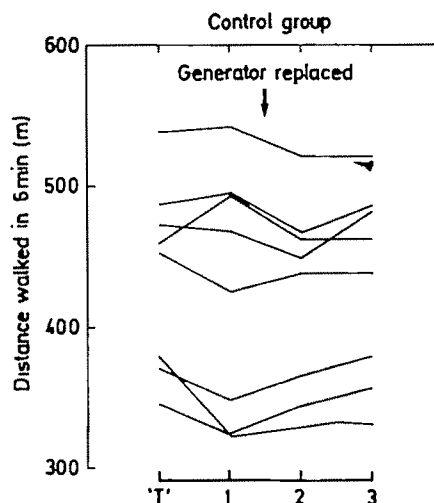


Fig 2 Results of 6 minute walks in eight control patients. T, "Training" walk; (1), immediately before pacing; (2), 48 h after pacing; (3), 1-12 months after pacing. Control group. T vs 1, 437.4 (66.1) vs 426.6 (83.7), NS; 1 vs 2, 426.6 (83.7) vs 429.3 (72.9), NS; 2 vs 3, 429.3 (72.9) vs 432.0 (67.5), NS. All distances are in metres ± 1 SD.

(86.4) m after pacing ($p < 0.001$). There was a further improvement in exercise capacity during the long term test (399.6 (86.4) vs 423.9 (89.1) m, $p < 0.05$). This test occurred at one month in eight patients, two months in two patients, three months in four patients, six months in two patients, eight months in one patient, and 12 months in one patient.

There was no significant age or sex difference between the study and control groups. No training effect was seen in the control group (fig 2); there was no significant difference in exercise capacity between the two walks before generator change (437.4 (66.1) vs 426.6 (83.7) m) and distances walked immediately before and after generator change were similar (426.6 (83.7) vs 429.3 (72.9) m). Exercise capacity remained unaltered on subsequent testing (429.3 (72.9) vs 432.0 (67.5) m).

SYMPTOMS

Ten of the 18 patients in the study group had to stop at least once and seven at least twice during their pre-pacing walks because of breathlessness or fatigue. Fifteen of the 18 patients felt breathless or exhausted at the end of their pre-pacing walks. In contrast, none of the patients needed to stop because of breathlessness or fatigue during their post-pacing walks and all felt less breathless at the end. The three patients with chronic airways disease who completed the study (cases 2, 8, and 11) showed an

improvement in their exercise capacity after pacing.

None of the patients in the control group needed to stop because of breathlessness during any of their walking tests, and exercise capacity was unaltered after replacement of their pacemaker generators.

FOLLOW UP

The 18 patients in the study group have been followed up regularly in the pacing clinic and 13 have been re-exercised, in some cases more than once, at least one year after being paced (table 1). Three patients (cases 1, 3, and 17) have died suddenly and a fourth (case 7) has had a left hemiparesis since entering the study. Patient 10 became mentally disturbed and has required admission to hospital so that it was not possible to repeat her walking test. The other patients in the study group remain in good health and have felt much better since being paced. The improvement in exercise capacity, as judged by walking distance, has been maintained in most of them, in some cases for up to 30 months after pacing. Exercise capacity was limited by arthritis in five patients and chronic airways disease in one, but nevertheless in four of these six patients it was better after pacing.

Discussion

The association between bradycardia and syncope had been noted by at least four observers, Marcus Gerbezius (or Verbez) of Laibach in 1719¹⁰ Giovanni Morgagni in 1769,¹¹ Thomas Spens in 1793,¹² and Sir William Burnett in 1824,¹³ before the publications of Robert Adams in 1827¹⁴ and William Stokes in 1846.¹⁵ The patients described by Morgagni¹¹ and Burnett¹³ both suffered, in addition, from paroxysmal nocturnal dysnoea and Robert Adams's¹⁴ patient had both syncope and cardiac failure.

Syncopal episodes, however, have tended to overshadow breathlessness as a typical symptom of heart block because of their dramatic nature and the abolition of symptoms by pacing.³ Nevertheless, some patients with heart block present with breathlessness or cardiac failure in the absence of syncope. The numbers are small; 23 (13%) of 174 with breathlessness and only six (3%) of 174 with cardiac failure in our series. Hetzel *et al* reported similar figures³; 21 of their 324 patients (6.5%) were in cardiac failure at the time of pacing. Although some series have reported a higher frequency of cardiac failure of 13–19%,^{16,17} it is uncertain how many of these patients also had syncope. Figures from the British Pacing Group indicate that 5.7% of patients are paced because of "heart failure",⁴ but this category has not been clearly defined and the numbers with

breathlessness without overt cardiac failure or syncope are unknown. They are small, perhaps reflecting a low referral rate for pacing in this group of patients. Those with syncope may be more likely to present to their doctor and their need for pacing more readily recognised.

Improvement in haemodynamic function after pacing has been demonstrated at least in some groups of patients. In the resting, unpaced state most patients with heart block have raised pulmonary artery and right heart pressures. Cardiac output is reduced despite an increased stroke volume.^{7,18,19} With ventricular pacing, resting right heart pressures fall, cardiac output increases, and stroke volume falls.^{5,7} Judge *et al* measured the effect of different pacing rates on cardiac output. Increasing heart rate from 60 to 75 beats per minute caused a 7% increase in cardiac output; there was little or no benefit from faster rates.²⁰ Since cardiac output had not been measured in the unpaced state, the effect of pacing remained uncertain. Sowton found two types of rate-output curves.⁵ In some patients cardiac output increased steadily with pacing from the idioventricular rate to a paced rate of about 70 beats per minute; further increases in pacing rate produced no further appreciable increase in cardiac output. A second group had an optimal rate at which cardiac output was maximal, with flow falling off sharply at rates on either side of this value. Optimal rates ranged from 56 to 90 beats per minute, most occurring in the 65 to 70 beats per minute range, and produced a 52% increase in resting cardiac output. Most patients had been paced because of syncopal episodes. Benchimol *et al* and Bevegard *et al* found increases in resting cardiac output of 67% and 60% respectively.^{6,7} In contrast, Gobel *et al* found that pacing increased cardiac output by only 17%,²¹ while Nager *et al* found an initial rise in cardiac output followed by a decline to pre-pacing levels within about 10 weeks of pacing.²² Most of the patients in these two studies were in congestive cardiac failure, however, and both groups concluded that the poor response to pacing was related to reduced left ventricular reserve.

In unpaced patients with heart block, heart rate increases little, if at all, with exercise, and cardiac output rises because of an increase in stroke volume.²³ With exercise at the optimal, paced heart rate Sowton found a mean increase in cardiac output from 4 to 10 litres per minute at least for short periods;⁵ Benchimol *et al* found an average 37% rise in cardiac index on exercise,⁶ and some of the patients studied by Bevegard *et al* were able almost to double their cardiac output.⁷ In their patients with congestive heart failure, Gobel *et al* found that cardiac output rose by a modest 28% with exercise.²¹

These haemodynamic studies suggest that in most patients with heart block, pacing will cause useful increases in cardiac output both at rest and on exercise. Our results showed a significant improvement in exercise capacity after pacing in patients whose presenting symptom was breathlessness. Breathlessness was reduced, and the improvement was maintained in some patients during a follow up period of up to 30 months. In six of 13 patients exercised more than one year after pacing the improvement in exercise tolerance, as judged by walking distance, was not maintained because of increasing locomotor disability (arthritis) in five and chronic airways disease in one; nevertheless four of them were better than before they were paced. These findings are in contrast with the reported outcome in patients in cardiac failure at the time of pacing. Bernstein *et al* found that pacing was of little value to their patients with heart block and congestive cardiac failure, and nine out of 22 patients died from heart failure within one year of pacing.¹⁶ Hetzel *et al* found a symptomatic improvement after pacing in only 10 out of 21 patients with cardiac failure, and haemodynamic improvement was demonstrated in only one of six patients studied invasively.³ In contrast, none of our patients was in overt cardiac failure at the time of pacing, and this may be the explanation for the improved outcome in our group. Patients with complete heart block effectively have a fixed heart rate and are dependent upon ventricular volume reserve for increases in cardiac output. In those with severe myocardial impairment volume reserve may be insufficient even to maintain cardiac output at rest, and cardiac failure ensues. It is perhaps not surprising that in this group increasing the heart rate to 70 beats per minute causes at best the modest resting haemodynamic improvement reported by Gobel *et al*²¹ with little or no useful increase in volume reserve, or that the short term haemodynamic benefits tend to become quickly decompensated.²² As a result pacing has little effect on exercise capacity or prognosis, which are both determined by the severity of myocardial disease. In patients with well preserved myocardial function and complete heart block, volume reserve may be used to prevent cardiac failure and to increase cardiac output on exercise. Increasing the (fixed) heart rate by pacing reduces resting end diastolic ventricular volume,⁵⁻⁷ leaving a greater volume reserve available for use during exercise. As a result, a larger increase in cardiac output may be achieved on exercise, and exercise capacity is increased. We believe that by selecting patients with breathlessness but no overt cardiac failure we have chosen those likely to benefit in this way from pacing.

Even among patients free from overt heart failure, however, there is likely to be a spectrum of myocardial impairment, and some patients may benefit little from pacing or even be harmed by it. We have shown that in those who benefit, an improvement is apparent 48 hours after pacing and may be confirmed objectively by a simple six minute walking test. No patient showing a substantial symptomatic improvement at 48 hours subsequently deteriorated. Thus if the potential long term benefit from pacing in any patient with heart block and breathlessness is in doubt, assessment by six minute walks before and during temporary cardiac pacing will provide an answer within 48 hours.

A six minute walk was chosen rather than bicycle or treadmill testing, which may frighten elderly patients and thus be an inaccurate or insensitive method of assessing their limited exercise capacity. The advantages of bicycle or treadmill testing are that it allows continuous electrocardiographic monitoring, and the use of graded exercise to limit the duration of tests in younger, fitter subjects. Neither feature was required for this study. We noted one important difference between our patients and those with chronic airways disease. In the latter group both McGavin *et al* and Guyatt *et al* showed a significant "training effect" between the first two walks and recommended two practice walks in each subject before starting any formal testing.^{8,24} We found no significant training effect either in the 10 patients in heart block who were exercised twice before pacing or in the eight controls whose exercise performance remained constant on four occasions over a four week period. It may be that the fixed heart rate and limited cardiac output in our patients prevented any appreciable training effect. Thus it appears that practice walks are not an essential requirement for the assessment of patients with heart block, but two walking tests are advisable to ensure a constant exercise performance before pacing. Use of a temporary pacemaker would also allow a subsequent test with the pacemaker switched off to confirm that any apparent benefit from pacing was lost when pacing was withdrawn. It is essential that in each patient all walking tests are supervised by the same observer to eliminate variations in performance caused by differing levels of encouragement offered by different observers.²⁴

We conclude that this simple six minute walking test can be used to identify those patients with breathlessness and heart block who will benefit from cardiac pacing. Benefit is more likely in those without overt cardiac failure, but where there is doubt a trial of temporary pacing is indicated.¹⁷ Breathlessness without syncope should not be considered a "soft" indication for cardiac pacing, which substan-

tially increased exercise capacity in most of our patients.

We thank Dr J Russell Rees, Dr S C Jordan, and Dr J Vann Jones for allowing us to study patients under their care.

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Value of the bipolar lead CM5 in electrocardiography

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SUMMARY Only bipolar lead recordings are available during ambulatory monitoring. Their sensitivity in detecting ST segment changes in relation to standard electrocardiographic leads is not known. The magnitude and direction of ST segment changes in the bipolar lead CM5 were compared with those in standard electrocardiographic leads in patients during exercise testing and percutaneous transluminal coronary angioplasty. Thirty patients with coronary artery disease were studied during exercise tests in which ST segment depression (>0.5 mm) occurred in one or more standard electrocardiographic leads and 13 patients were studied during angioplasty that resulted in ST segment change in one or more leads (I, II, III, V2, V5, and CM5). Lead CM5 was the most sensitive lead (93%) during exercise testing and also showed the greatest magnitude of ST segment change below the isoelectric line in 93% of the patients. Only two patients, one with ST segment elevation in inferior leads and one with changes restricted to septal leads, had no ST segment depression in lead CM5. When ST segment shift from the baseline electrocardiogram was measured the magnitude of depression was greatest in lead CM5 in only 63% of the patients. During angioplasty of the left anterior descending coronary artery, lead CM5 showed ST segment depression in seven patients, ST segment elevation in two, and a biphasic response in one. Two of the three patients with balloon inflation in the right coronary artery developed ST segment elevation in lead CM5.

Thus lead CM5 is a reliable lead for detecting subendocardial ischaemia experienced during everyday activities in anginal patients. During total occlusion of coronary arteries (as in variant angina or myocardial infarction) lead CM5 commonly shows ST segment depression and changes due to right coronary artery occlusion may not be detected.

Ambulatory monitoring is increasingly being used to detect ST segment changes.¹⁻³ Most modern systems provide two channel recordings only, which are obtained from bipolar leads and one of the leads most commonly recorded is CM5. It is, therefore, important to determine the value of lead CM5 compared with that of other conventional electrocardiographic leads used in the detection of ST segment changes, especially to see whether there are specific patterns of ST segment change during conventional 12 lead electrocardiography which would remain undetected if CM5 alone were used. Using exercise testing as a model of subendocardial ischaemia and transluminal angioplasty as a model

of transmural ischaemia, we studied the ST segment changes in lead CM5 and compared them with those in conventional electrocardiographic leads.

Patients and methods

PATIENTS

Two groups of patients were studied. Group 1 consisted of 30 patients, 24 men and six women (mean (SD) age 54 (9) years) who were undergoing routine angiocardiology for chest pain. All patients had important coronary artery disease, defined as $>70\%$ luminal narrowing of one or more major coronary arteries and ST segment depression >0.5 mm at the end of exercise. Nine patients had single vessel coronary artery disease, nine had two vessel disease, and 12 had three vessel disease. Patients were exercised after giving informed consent. Seven patients were on β adrenoceptor antagonist treatment. Group 2

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consisted of 13 patients who underwent coronary angioplasty; 10 had proximal left anterior descending coronary artery stenosis only and three had single right coronary artery stenosis. There were 10 men and three women (mean (SD) age 52 (8) years). Continuous six lead electrocardiographic recording was performed during percutaneous transluminal coronary angioplasty and all patients had ST segment changes in at least one electrocardiographic lead.

EXERCISE TESTING

Group 1 patients performed a maximal symptom limited exercise test. A 12 lead electrocardiogram was recorded at the end of each stage and lead CM5 was substituted for lead aVR. The patients exercised on a bicycle ergometer at 50 revolutions per minute and the workload was increased every three minutes so that there was an increase in heart rate of at least 10 beats a minute at each stage. The tests were stopped when anginal chest pains, frequent ventricular extrasystoles, important ST segment depression (>3 mm), a fall in blood pressure, or exhaustion developed.

The electrocardiogram was recorded on an ink jet recorder (Siemens Mingocard 7). The indifferent electrode of lead CM5 was placed over the manubrium and the active electrode was on the precordial V5 position. ST segment change was measured accurately by means of a magnifying lens with a graticule marked in 0.1 mm divisions (Flubacher, Switzerland). A line drawn between two consecutive PR segments gave the zero baseline. ST segment change was measured 0.08 s after the J point.

ELECTROCARDIOGRAPHIC RECORDING DURING ANGIOPLASTY

In group 2 patients a continuous six lead electrocardiogram (I, II, III, CM5, V2, and V5) was recorded with the patient in the supine position

before, during, and after balloon inflation. ST segment change was measured with a magnifying lens as described above and only patients with ST segment depression or elevation of ≥ 0.5 mm from the baseline electrocardiogram were included in this study.

Results

COMPARISON OF CONVENTIONAL ELECTROCARDIOGRAPHIC LEADS WITH LEAD CM5 DURING EXERCISE TESTING

Twenty eight (93%) of 30 group 1 patients developed >0.5 mm ST segment depression below the isoelectric line in lead CM5 and this was the most sensitive of the 12 leads monitored in this study. In comparison, ST segment depression of >0.5 mm occurred in 70% of patients in lead V6, 67% in lead V5, 43% in lead V4, and 50% in lead II (table). In 93% of patients lead CM5 also showed the greatest depression of the ST segment below the isoelectric line (table). In the remaining two patients, lead V5 and V2 respectively demonstrated the maximum ST segment depression. In these patients, although ST segment depression occurred in lead CM5, it was <0.5 mm. ST segment depression was 1.4 (0.9) (mean (SD)) in lead CM5 in the 28 patients in whom important depression developed. In comparison the magnitude was 1.2 (0.5) mm (mean (SD)) in the 21 patients with important depression in lead V6 and 1.45 (0.6) in 20 patients with important depression in lead V5. Only 25 patients fulfilled the conventional criterion of 1 mm ST segment depression 0.08 s after the J point at the end of exercise in one or more leads. Lead CM5 showed the maximum ST segment depression in 23 (92%) of these 25 patients.

In 17 patients ST segment depression was observed in two or more of the inferior leads (II, III, aVF) as well as the anterolateral leads (V4, V5, V6). Of the remaining 13 patients, 11 had changes in the

Table Number of patients who developed ST segment depression of varying magnitude from the isoelectric line in the 12 electrocardiographic leads during bicycle ergometry

Leads	Patients with ST depression				Maximum ST depression
	≥ 2 mm	<2 – ≤ 2 mm	>0.5 – 1.0 mm	<0.5 mm	
I	0	1	4	1	0
II	1	8	6	8	0
III	0	3	4	5	0
aVL	0	0	0	5	0
aVF	0	4	6	5	0
V1	0	0	0	0	0
V2	1	1	1	0	1
V3	1	1	3	0	0
V4	1	6	6	2	0
V5	2	10	8	2	1
V6	1	7	13	3	0
CM5	5	18	5	2	28

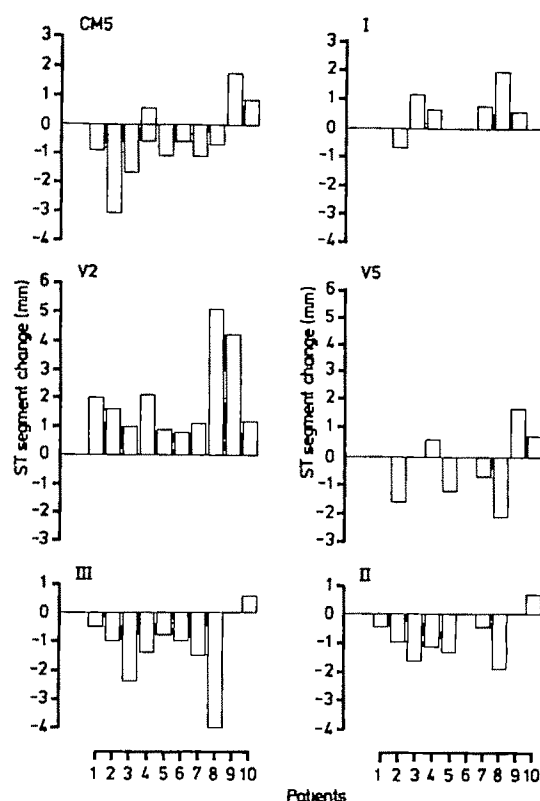


Fig 1 Magnitude and direction of ST segment changes in lead CM5 and other standard electrocardiographic leads in 10 patients with single vessel disease during balloon inflation in the left anterior descending coronary artery.

anterolateral leads only, one in leads V2 and V3 only, and another in lead II only. Only one patient with an old inferior myocardial infarction developed ST segment elevation in inferior leads during exercise. All other patients either showed depression or had no shift of the ST segment with exercise. The patient with ST segment elevation in the inferior leads during exercise showed a smaller change in lead CM5 than in leads V5 and V6.

When ST segment shift from the baseline electrocardiogram was examined instead of the shift from the isoelectric line as described above, lead CM5 showed greater or equal magnitude of ST segment depression compared with standard electrocardiographic leads in 19 (63%) patients. In none of the patients was ST segment change confined to the inferior leads. Even the two patients with isolated right coronary artery stenoses had electrocardiographic changes in leads V5 and V6 in addition to changes in the inferior leads.

COMPARISON OF CONVENTIONAL ELECTROCARDIOGRAPHIC LEADS WITH CM5 DURING ANGIOPLASTY

During left anterior descending coronary artery occlusion leads V2 and CM5 were the most sensitive in detecting ST segment change (fig 1). In lead CM5 seven patients had ST segment depression, two had ST segment elevation, and one patient had ST segment depression progressing to ST segment elevation during balloon inflation (fig 1). Changes in the ST segment occurred approximately at the same time in all the leads in individual patients and the mean (SD) duration of onset was 15 (12)s after balloon inflation.

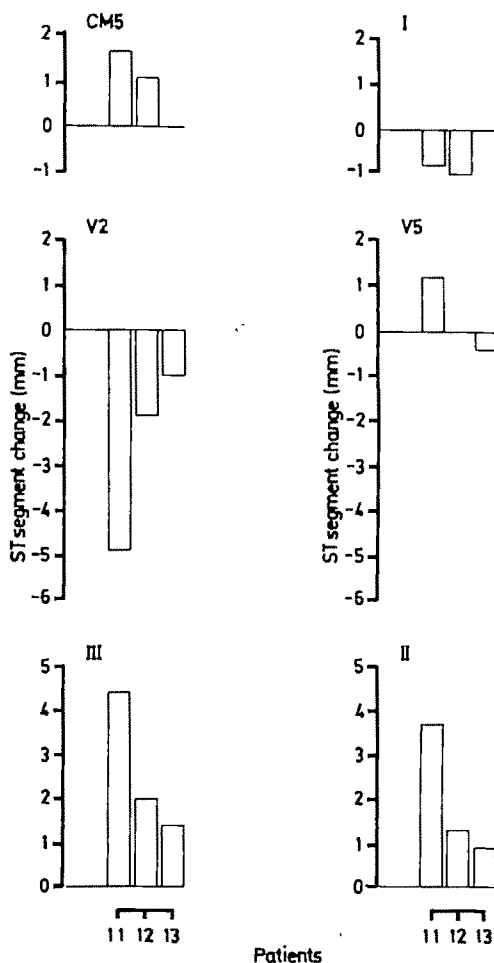


Fig 2 Magnitude and direction of ST segment changes in the lead CM5 and other standard electrocardiographic leads in three patients with single vessel disease during balloon inflation in the right coronary artery

During balloon occlusion of the right coronary lumen in three patients, ST segment elevation occurred in the inferior leads II and III and this was accompanied by ST segment depression in lead CM5 in two patients (fig 2).

Discussion

Multiple lead electrocardiography is more sensitive than single lead systems for detecting coronary artery disease by stress testing.⁴⁻⁶ The addition of lead CM5 increases the sensitivity further.^{4,6} When only bipolar lead analysis is available, however, as in ambulatory ST segment monitoring it is important to determine which lead or leads are most likely to demonstrate ST segment change. Although in this study we have confirmed that lead CM5 is the most sensitive electrocardiographic lead during exercise testing,^{4,6} further information is required on its usefulness in relation to conventional electrocardiographic leads in various clinical situations. For this purpose we selected patients who had ST segment depression during stress testing in at least one of the standard electrocardiographic leads and correlated the changes observed in lead CM5 with changes in the other leads. We thus attempted to identify patients in whom important ST segment changes occur during multiple lead electrocardiography but are not reflected in lead CM5.

There are two common patterns of myocardial ischaemia. Angina on exertion usually results from subendocardial ischaemia and causes ST segment depression on the surface electrocardiogram, a situation reproduced during exercise testing. Transmural ischaemia may result from severe coronary spasm or thrombotic occlusion of a major coronary vessel, and balloon inflation in the coronary artery will have a similar effect. Ischaemia results in ST segment elevation in the territory of the artery occluded. We evaluated the usefulness of ST segment changes in lead CM5 in these two situations. We found that ST segment changes in lead CM5 occurred in 93% of all patients who were exercised and in 100% of patients who developed anterolateral and inferior wall ischaemia during exercise. It was only unreliable in a patient with previous inferior wall infarction and ST segment elevation during exercise and in another patient who developed changes in leads V2 and V3 only. During angioplasty, complete occlusion of the coronary lumen of the left anterior descending coronary artery resulted in ST segment change in all patients in lead CM5. The direction of change was variable, however, and occasionally bidirectional. With right coronary artery occlusion, one of the three patients did not develop significant ST segment change in lead CM5

although there was ST segment elevation in the inferior leads (fig 2).

Depression below the arbitrary isoelectric line is conventionally used in the visual analysis of ST segments. By this criterion the greatest ST segment depression was found in lead CM5 in 93% of the patients. When the shift of the ST segment from the resting electrocardiogram was analysed, in 39% of the patients the change was greater in leads other than CM5. Thus, although the depression of ST segments may be more obvious in lead CM5, the rate of ST segment depression is often greater in other electrocardiographic leads which do not demonstrate the greatest magnitude of ST segment depression below the isoelectric line.

There were no significant differences between the magnitude of ST segment depression in lead CM5 and the presence or absence of inferior ST segment depression. In one patient, however, in whom there was ST segment elevation in the inferior leads on exercise and >1 mm ST segment depression in lead V5, lead CM5 showed unimportant (<0.5 mm) ST segment depression. It has been suggested that lead CM5 has components from both inferior and anterolateral myocardial walls⁷ and if differing directional changes occur in these two areas, there may be little change in lead CM5. This is borne out to some extent by the electrocardiographic changes observed during angioplasty of the left anterior descending coronary artery. Here lead III often showed ST segment depression and lead V2 had ST elevation and lead CM5 demonstrated ST depression, ST elevation, or a biphasic response.

Thus although CM5 is a reliable lead for detecting the common type of exertional ischaemia in most patients, it may not detect ischaemia in those with previous inferior myocardial infarction and where changes are restricted to anteroseptal (V1, V2, V3) leads. In patients with coronary spasm, in the left anterior descending or right coronary arteries the change in lead CM5 is usually ST segment depression but is sometimes bidirectional; therefore the absence of ST segment elevation in lead CM5 does not imply absence of occlusion of the coronary arteries. Furthermore, in this situation, lead CM5 often does not demonstrate the maximum ST segment shift and may not be the ideal lead (figs 1 and 2). When spasm is present a bipolar lead CM2 may be more suitable for detecting septal ST segment changes and a bipolar lead resembling lead II^{4,6} may be more suitable for detecting inferior wall ischaemia.

Therefore, if two bipolar leads are available for ambulatory monitoring, CM5 would certainly be the most useful first lead. The choice of the second lead should depend on other clinical factors such as

detection of spasm or demand angina and electrocardiographic factors such as the presence of an old inferior infarction. Use of bipolar leads resembling those in which the exercise test is most positive would also improve the sensitivity of the technique.

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Quyyumi, Crane, Mockus, Wright, Rickards, Fox

Case reports

Angioplasty of an occluded left anterior descending coronary artery: usefulness of retrograde opacification of the distal part of the occluded vessel via the contralateral coronary artery in positioning the balloon catheter

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SUMMARY A 59 year old man was admitted to hospital with a non-transmural anterior myocardial infarction. Recurrent angina pectoris eight days after the initial infarction was investigated by cardiac catheterisation, which showed moderate anterior hypokinesia and proximal occlusion of the left anterior descending coronary artery. The distal part of this vessel was opacified via collaterals from the right coronary artery. Percutaneous transluminal coronary angioplasty was attempted during the same catheterisation; good positioning of the balloon catheter was confirmed by the use of retrograde opacification of the distal part of the left anterior descending coronary artery via the collateral vessels and dilatation was safely achieved.

Opacification of the contralateral coronary artery may be a useful and safe positioning of guide wire system or balloon dilatation catheter when dilatation of a totally occluded coronary artery is attempted.

Use of a movable guide wire system facilitates successful percutaneous transluminal coronary angioplasty when the coronary artery is occluded. When collateral vessels, which usually arise from the contralateral coronary artery, are present the myocardium may remain viable despite a coronary occlusion. Such vessels also allow visualisation of the distal part of the occluded vessel. This retrograde opacification of the occluded vessel may be useful for the safe positioning of either the guide wire or the balloon catheter before inflation. We report the retrograde visualisation of an occluded left anterior descending coronary artery via collateral vessels from the right coronary artery. This allowed good positioning of the balloon catheter and

safe percutaneous transluminal coronary angioplasty.

Case report

A previously healthy 59 year old patient was admitted to the coronary care unit in August 1985 with prolonged chest pain. The patient had no previous history of coronary disease. Examination of the heart was normal and the electrocardiogram showed ST segment depression in the anterior leads from V3 to V6 and in the inferior leads but without pathological Q wave. Echocardiographic examination showed a moderate anterior hypokinesia. Chest pain and ST segment depression persisted despite sublingual and intravenous nitrates. Peak plasma concentration of creatine kinase was 850 U/l (creatin kinase MB 8%) twelve hours after admission and the chest pain resolved. Serial electrocardiograms did not show

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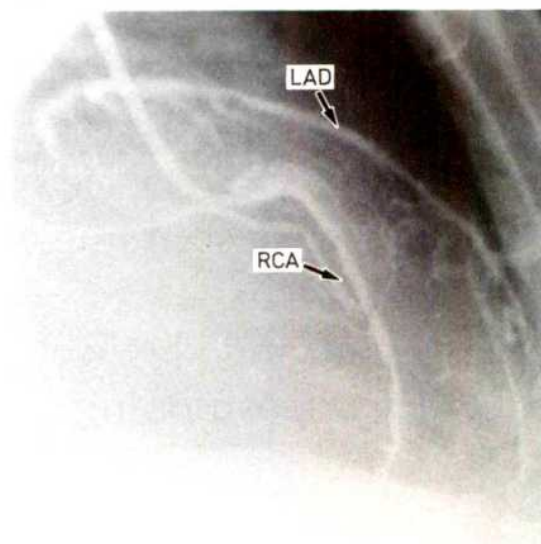


Fig 1 Angiography of the right coronary artery produced opacification of the distal part of the left anterior descending coronary artery (LAD) via collateral vessels arising from the right coronary artery (RCA).

any abnormal Q waves and the ST segment abnormalities completely regressed. A non-transmural anterior myocardial infarction was diagnosed. Because the patient later had spontaneous recurrent chest pain with ST segment depression in the elec-

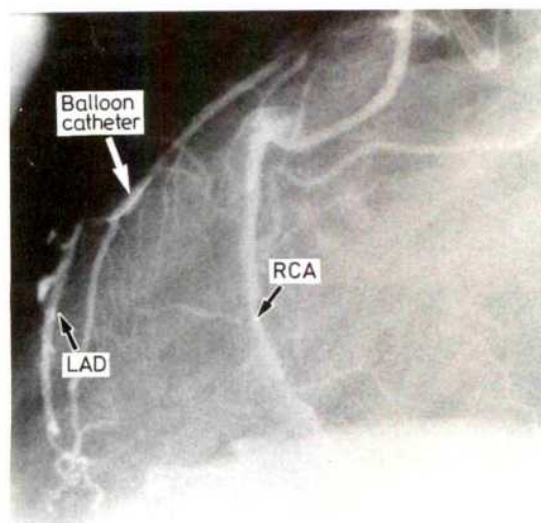


Fig 2 Position of the balloon dilatation catheter demonstrated by the retrograde opacification produced by contrast coming from the right coronary artery via collateral vessels.

trocardiographic anterior leads a cardiac catheterisation was performed eight days after admission. This showed impaired left ventricular function with anterior hypokinesia and an ejection fraction of 45%. The left anterior descending coronary artery was occluded at the origin of the first septal perforator. During angiography of the right coronary artery there was a rapid retrograde filling of the left anterior descending coronary artery through large collateral vessels (fig 1). Coronary angioplasty was attempted from the right femoral approach with a 9 French Judkins-type guiding catheter and 3 mm balloon dilatation catheter. Simultaneous opacification of the right coronary artery obtained with a 8 French Judkins catheter from the left femoral approach allowed the distal part of the left anterior descending coronary artery to be visualised and the balloon dilatation catheter to be well positioned in the occluded artery (fig 2). Angioplasty was then performed safely and without difficulty on the mid and proximal part of the left anterior descending coronary artery. Chest pain did not recur after the procedure.

Discussion

Percutaneous transluminal coronary angioplasty during the acute stage of myocardial infarction (with or without intracoronary or intravenous fibrinolysis) allows prompt recanalisation in a high proportion of cases even when there is occlusion of the infarct associated coronary artery.¹⁻³ According to Pepine *et al*² the reason for the high success rate in these circumstances is that penetration of the balloon catheter or the movable guide wire through the occluded vessel is easier than in chronic angina because the material causing occlusion (both old and fresh thrombus and other mechanical elements) is softer and more easily dilated at low pressures. In patients with acute myocardial infarction visualisation of the distal part of the occluded coronary artery via collateral vessels from the contralateral vessel is rare.⁴ Conversely patients with chronic coronary artery obstruction and preservation of myocardial function often have an important collateral flow arising from the ipsilateral or contralateral coronary arteries or both. Elective percutaneous transluminal coronary angioplasty of a totally occluded coronary artery not associated with myocardial infarction is equally feasible.^{5,6} The primary success rate is about 54% (conventional stenoses 85%),⁶ but it varies according to the duration of occlusion (success rate 65% when the occlusion is estimated to have been present for $\leq$ eight weeks and 44% for $>$ eight weeks) and whether there is a "functionally occluded vessel" that is not totally

occluded or "total vessel occlusion."⁵ Contrast clears from the collateral vessels immediately after successful percutaneous transluminal coronary angioplasty.⁶ Safe coronary angioplasty needs good visualisation of the coronary artery that is to be dilated and for this reason it may be difficult to position the balloon dilatation catheter when the vessel is totally occluded. Like MacDonald and Feldman⁷ we found that good opacification of the post-occlusive part of the coronary artery was obtained via the contralateral vessel. We agree with the previous report⁷ that retrograde distal opacification of the occluded coronary artery via a collateral vessel is useful for good positioning of the guide wire and the balloon catheter during percutaneous transluminal coronary angioplasty.

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Congenital diverticulum of the heart arising from the coronary sinus

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SUMMARY A diverticulum originating from the coronary sinus was diagnosed by echocardiography in a two day old baby with hypoplastic left heart. At necropsy the diverticulum was seen to arise from the coronary sinus and it penetrated the right ventricular posterior wall.

Congenital diverticula of the heart have been reported to arise from the atria¹ or from the ventricles.^{2,3} We report on a diverticulum arising from the coronary sinus at its junction with the right atrium in a neonate with a hypoplastic left heart.

Case report

A 3.55 kg girl was born by normal delivery at the 39th week of a normal gestation. When she was two days old she was referred for cardiological evaluation because of mild cyanosis. Arterial PO₂ was 42 mm Hg. Physical examination showed a grade 2/6 high pitched pansystolic murmur and a single second heart sound. The peripheral pulses were normal at the first examination, but became weak on the third day of life. An electrocardiogram showed right ventricular hypertrophy and a chest x ray showed a bulge at the left cardiac border.

Cross sectional echocardiography was performed when she was two days old. The left atrium, the left ventricle, the aortic root, the aortic valve, and the ascending aorta were all hypoplastic. The mitral valve was atretic and a small interventricular septal defect was also seen. In the parasternal long axis view a large cavity was seen behind the left ventricle; above this was a large coronary sinus (fig 1a). The external wall of the cavity was approximately the same thickness as the atrial wall and did not contract appreciably; its floor was formed by ventricular wall. In the subcostal view we identified a hypoplastic left

atrium receiving the pulmonary veins. The right atrium was enlarged, and a very large coronary sinus was demonstrated. The ostium of the coronary sinus was widely patent. A standard four chamber posterior view showed that the accessory cavity was caudal to the coronary sinus and the right atrium (fig 1b). This diverticulum was divided into two by a membrane; the left part of the diverticulum was about twice the size of the right one and was connected to the coronary sinus by an opening of about 6 mm in diameter located on the floor of the coronary sinus at its junction with the right atrium. Contrast echocardiography was undertaken after injection of 2 to 3 ml of 5% dextrose into a left antecubital vein. Because the contrast echoes entered the heart from the coronary sinus a persistent left superior vena cava connected to the coronary sinus was diagnosed. The contrast material then entered the right atrium and the left portion of the diverticulum and thereafter the right part of the diverticulum.

Cardiac failure with cardiogenic shock progressively developed and the infant died when she was four days old.

PATHOLOGY

Macroscopic examination of the heart showed a bulge 2.5 × 2 cm on the posterior aspect of the ventricles (fig 2a). The right atrium, the right ventricle, and the pulmonary artery were enlarged; the ductus arteriosus was widely patent; the left atrium was severely hypoplastic, but normally connected to four pulmonary veins; the foramen ovale was patent. The mitral valve was atretic and the hypoplastic left ventricle communicated through a small ventricular septal defect with the right ventricle. The ascending aorta up to the isthmus was also hypoplastic. A

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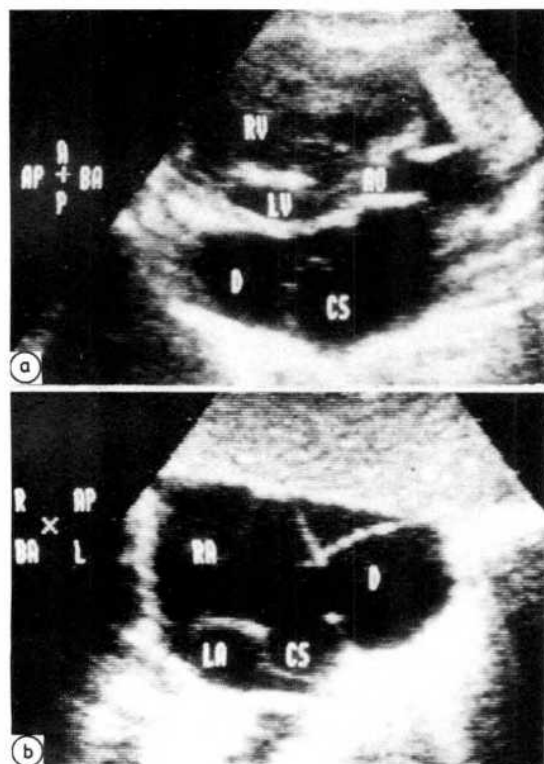


Fig 1 Cross sectional echocardiograms. (a) In the parasternal long axis view a diverticulum is seen behind the hypoplastic left ventricle and below the enlarged coronary sinus. (b) In the transversal subcostal view with posterior orientation of the transducer the large diverticulum is seen to be divided into two portions by a membrane. The left atrium is hypoplastic and the coronary sinus is enlarged. There is a connection between the diverticulum and the coronary sinus. AO, aorta; CS, coronary sinus; D, diverticulum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

persistent left superior vena cava entered a very large coronary sinus. The ostium of the coronary sinus was patent and the thebesian valve was absent. An opening of about 6 mm in diameter on the floor of the coronary sinus just before its junction with the right atrium led into the left chamber of a diverticulum (fig 2b). The diverticulum lay behind the right ventricle and behind and to the right of the hypoplastic left ventricle; its superior border reached the atrioventricular groove below the coronary sinus (fig 2a) and its inferior border was 8 mm from the cardiac apex. The external surface of the diverticulum was covered by epicardium and by epicardial vessels continuous with the epicardial vessels of the ventricles. The diverticulum was divided into two cavities by a fenestrated membrane (fig 2c); the

left cavity was about twice as big as the right, being connected to the coronary sinus through a hole in the upper portion of its floor; the only openings of the right cavity were the fenestrations of the diverticular septum. The floor of the diverticulum was formed by trabeculated muscle covered by a smooth endocardium; the free wall was 0.5 mm thick.

Microscopic examination showed that the floor of the diverticulum was formed by normal myocardium covered by endocardium. Its free wall was composed of a layer of thin myocardial fibres, normal endocardial lining, and normally vascularised and innervated epicardium on the external surface (fig 2d). The septum of the diverticulum was formed by thin myocardium lined on both sides by endocardium.

Sections of the wall of the coronary sinus itself showed a well developed and oriented myocardial layer with a thin myocardium and a well vascularised epicardium with very scanty fatty tissue.

Discussion

Congenital diverticula of the heart are rare anomalies that usually arise from the left ventricle. They have been found on the basal aspect of the left ventricle⁴ or on the apex.^{2,5} Diverticula on the apex usually occur as part of a syndrome of cardiac anomalies and midline defects. The walls of these congenital left ventricular diverticula are formed by normal ventricular myocardium. Subvalvar left ventricular aneurysms, principally occurring in the Bantu and characterised by extensive fibrosis of the walls, with a suggested congenital^{6,7} or acquired aetiology have also been described.⁷

Right ventricular diverticula are extremely rare.³ They are occasionally associated with a left ventricular diverticulum.³ Only three cases of a congenital diverticulum arising from the right ventricle alone have been reported.^{3,8} These diverticula appeared as large outpouchings of the right ventricular cavity at the apex⁸ or at the base of the ventricle.³

Congenital aneurysms of the atria have also been reported.^{1,9,10} These are usually found in the appendage of the left⁹ or of the right atrium.¹⁰

Congenital anomalies of the coronary sinus include enlarged coronary sinus as a result of anomalous connection to the coronary sinus of systemic or pulmonary veins and fenestration or absence of the coronary sinus.¹¹⁻¹³ Fenestration of the coronary sinus ("partially unroofed coronary sinus") creates a communication between the atria and provides a route for blood to flow from one atrium to the other when an atretic atrioventricular valve is present.¹²

The diverticulum in our patient differs from the

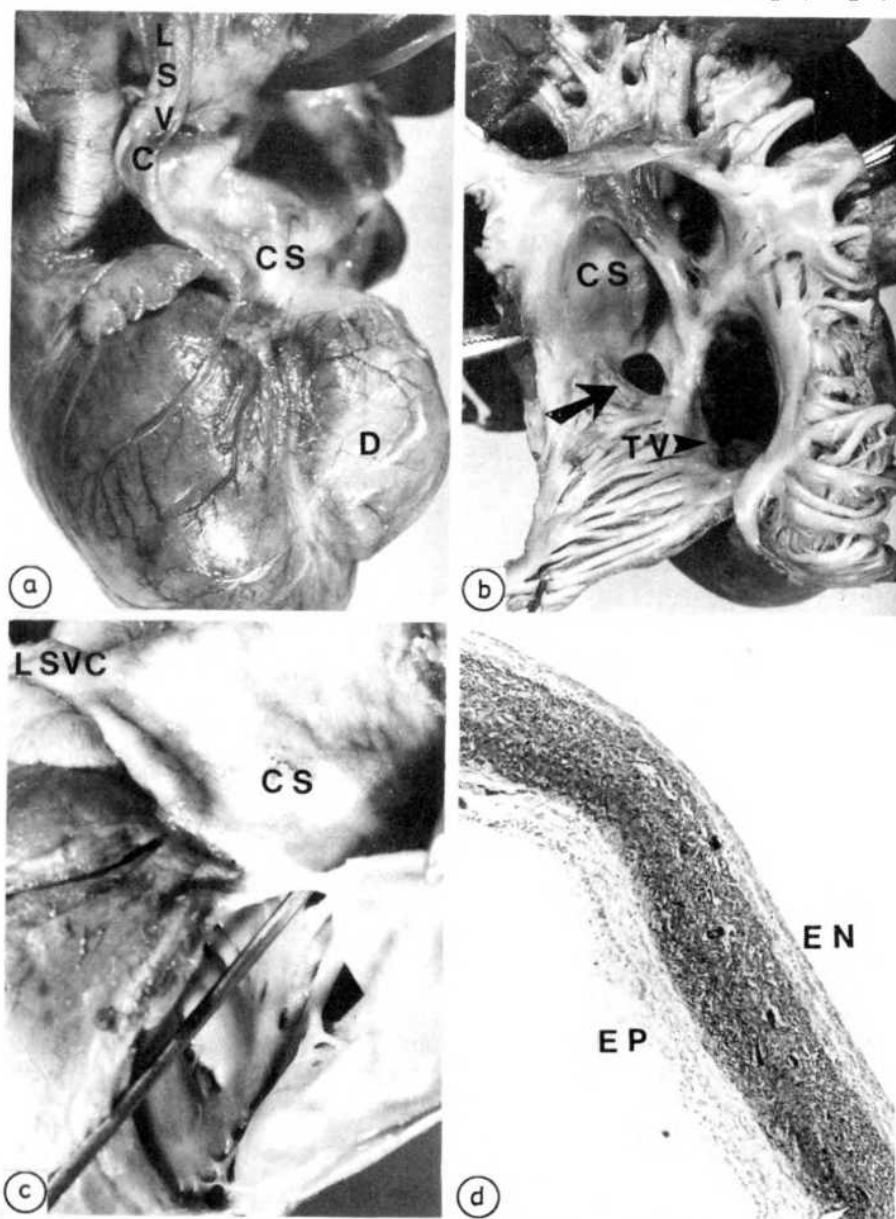


Fig 2 Pathology of the heart. (a) External view of the heart from its left side showing a 2.5 cm long diverticulum located below the atrioventricular groove and behind the ventricles. The large structure above the diverticulum is the coronary sinus, which is connected to the left superior vena cava. (b) Internal view of the right atrium. The ostium (arrow) of the diverticulum (6 mm in diameter) is within the coronary sinus immediately before its connection to the right atrium. (c) Internal view of the right and larger portion of the diverticulum. The floor of the diverticulum is formed by trabeculated right ventricular muscle lined by endocardium. The septum of the diverticulum is fenestrated. The free wall of the diverticulum is 0.5 mm thick. A probe is inserted in the opening between the diverticulum and the coronary sinus. (d) Microscopic appearance of the free wall of the diverticulum. The myocardial layer is covered by epicardium and internally by endocardium. Masson stain. EN, endocardium; EP, epicardium; L.SVC, left superior vena cava; TV, tricuspid valve; other abbreviations as in fig 1.

anomalies described above and probably resulted from a developmental defect. It can be distinguished from a false aneurysm of inflammatory or traumatic origin because there were well developed striated myocardial fibres and no fibrous tissue in all portions of its walls. It may be a true diverticulum of the coronary sinus: the presence of myocardial fibres in its walls does not rule out this diagnosis because the coronary sinus is part of the cardiac venous system and, as with other juxtacardiac segments of veins (and as found in our case), myocardial fibres may be present in its walls.¹⁴ If this anomaly does indeed represent a true diverticulum of the coronary sinus one would expect to see similar histological components through the entire circumference of its walls. In our case, however, the floor of the diverticulum clearly belonged to the right ventricular wall. The free wall of the diverticulum was formed by thinned myocardium normally overlaid by pericardium and internally lined by endocardium. Its floor was formed by the normal right ventricular myocardium lined by endocardium; we believe the diverticulum was the result of a dissection within the right ventricular external wall.

A dissection of the right ventricular free wall could be the result of a primary event leading to the formation of a cavity that tracks to the coronary sinus and penetrates into the heart cavities. Cases of subvalvar aneurysm originating within the left ventricular wall and extending into the left atrium have been reported.⁷ In these cases extensive fibrosis, calcification, and even ossification of the left ventricular wall were found. In our case, however, there was no evidence of degenerative or inflammatory processes affecting the myocardium and leading to the formation of a cavity. There are no reported examples of a primary congenital dissection of the myocardium. Thus it seems most probable that this diverticulum originated from the coronary sinus and then penetrated into the right ventricular wall. Defects in the walls of the coronary sinus, although rare, have been reported,^{11,13} and we assume that a deficiency in the floor of the coronary sinus during fetal life by an undetermined cause resulted in the formation of a sac which made its way through the right ventricular myocardium.

In our case the coronary sinus was enlarged and was connected to a persistent left superior vena cava; mitral atresia with a hypoplastic left ventricle and aorta were also present. Previously reported fenestrations of the coronary sinus associated with mitral atresia occurred on the floor of the coronary sinus and allowed an accessory route for blood to flow from the left atrium.^{11,12} In our case the opening was on the free wall of the coronary sinus, which is at variance with other reported defects; it did not con-

nect the left atrium to the right atrium and so did not play any functional role in relieving the left atrio-ventricular obstruction.

The diverticulum in our patient was clearly diagnosed by cross sectional echocardiography. The echocardiographic appearance of the diverticulum exactly matched the pathological features and allowed the *in vivo* diagnosis of this bizarre anomaly. Clinical recognition of this anomaly did not influence the management of our case because of the severe associated anomaly of hypoplastic left heart, for which only experimental treatment is available in few selected centres throughout the world. It is, however, possible that an isolated diverticulum could be surgically repaired. Successful resection of cardiac diverticula has been reported.^{2,9} Untreated diverticulae may rupture, be a source of embolisation, or produce cardiac failure and arrhythmias.

We have described a previously unreported congenital cardiac anomaly—a diverticulum originating from the coronary sinus. The excellent correlation between the echocardiographic and pathological findings means that this anomaly may be readily diagnosed once the possibility of its existence is known.

We thank Dr Jesse E Edwards for his advice in interpreting the pathological findings.

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Left ventricular outflow tract obstruction due to anomalous mitral valve: successful mitral valve replacement in a four month old infant

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SUMMARY A four month old infant who was investigated for heart failure was found to have mitral incompetence and severe subvalvar aortic stenosis. The left ventricular outflow tract obstruction was found to be due to an anatomically anomalous mitral valve. The obstruction could only be relieved by removal of the mitral valve and its replacement with a St Jude's prosthesis. Two years after operation the child is fit and active. There have been no difficulties with anticoagulant treatment.

In 1957 Ferencz reported an infant with mitral incompetence and left ventricular outflow tract obstruction caused by anatomical malformation of the subvalvar apparatus of the mitral valve.¹ Since then there have been many excellent necropsy studies, but few clinical reports, of mitral valve abnormalities in which left ventricular outflow tract obstruction was demonstrable in conjunction with mitral stenosis or mitral incompetence. We report a case of severe mitral incompetence and subvalvar aortic stenosis in an infant in whom obstruction of the left ventricular outflow tract was caused by disorganised structure of the subvalvar apparatus of the mitral valve. This obstruction could only be relieved by replacement of the mitral valve. There are few reports of mitral valve replacement in infancy. This child has done well during a two year follow up.

Case report

The patient was born at 41 weeks' gestation by lower segment caesarean section for fetal distress. He weighed 3.6 kg. Soon after birth a systolic murmur was heard, which was thought to be caused by a small ventricular septal defect. He appeared to thrive and was sent home at 10 days to be followed

up as an outpatient. When he was four months old he was readmitted to the referring hospital with a 24 hour history of poor feeding. He was severely dyspnoeic and was found to be in heart failure. On transfer to this unit he was extremely tachypnoeic with bulging precordium, subcostal recession, and hepatomegaly. The auscultatory findings were consistent with severe mitral incompetence and a chest radiograph showed pulmonary oedema with enlargement of the left atrium and left ventricle. The electrocardiogram showed left atrial and left ventricular hypertrophy. The cross sectional echocardiogram showed a vigorously contracting left ventricle and dilated left atrium. The possibility of hypertrophic obstructive cardiomyopathy was raised but the hypertrophy appeared to be localised to the mid-cavity. Both leaflets of the mitral valve were visualised and were thought to be normal. The aortic valve was bicuspid. The infant did not improve on nasogastric feeding and a vigorous anti-failure regimen, so one week later cardiac catheterisation and angiography were carried out. This confirmed severe mitral regurgitation but in addition a gradient of 90 mm Hg was recorded across the left ventricular outflow tract. The aortic valve appeared to be bicuspid and stenotic and angiography of the left ventricle demonstrated gross mitral incompetence into a huge left atrium. The left ventricle was contracting vigorously and the appearance resembled that of hypertrophic obstructive cardiomyopathy. There appeared to be localised nar-

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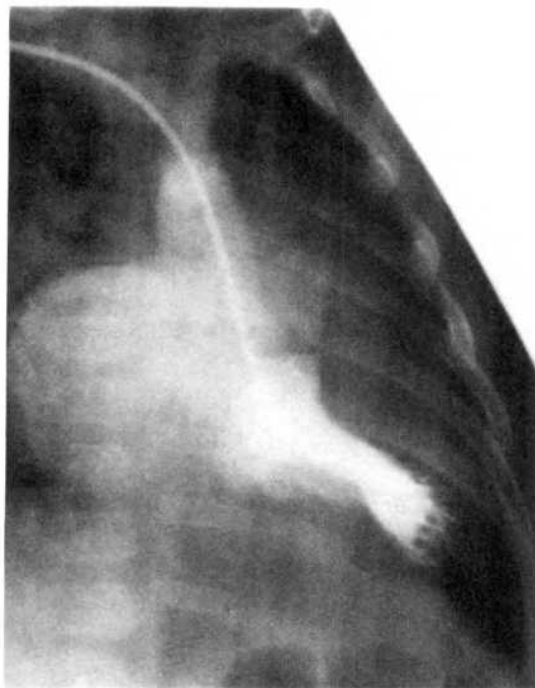


Fig 1 Left ventricular cineangiogram (end systolic frame) showing severe mitral incompetence into a large left atrium. The left ventricle shows a "waisted" appearance in the mid cavity.

rowing in the mid-cavity, however (fig 1). There was some discussion as to whether the obstruction was valvar or subvalvar but because of his clinical condition he was referred for exploration of mitral and aortic valves and the subaortic area.

SURGICAL FINDINGS

The child was operated on by Mr R N Sapsford with cardiopulmonary bypass and cold potassium cardioplegia for myocardial protection. The aortic valve

was bicuspid but not obviously stenosed. The mitral valve, however, was grossly abnormal and unusual in appearance. The annulus was dilated with normal leaflets, but the chordae tendineae were much shortened and inserted directly into sheets of fibrous tissue. There were no recognisable papillary muscles. The tissue supporting the anterior leaflet obstructed the left ventricular outflow tract. There was no generalised endomyocardial fibrosis and the ventricle contracted well. There was a patent foramen ovale and the ventricular septum was intact. In an attempt to avoid mitral valve replacement, a Wooler type mitral annuloplasty was performed and the areas of fusion of the aortic cusps were divided. The major cause of the severe left ventricular outflow tract obstruction was subvalvar and was caused by the abnormal subvalvar apparatus of the mitral valve. Some obstructing tissue was excised from the left ventricular outflow tract but fenestration of the tissue was not feasible. Despite some reduction in the severity of the mitral incompetence, the infant remained in left ventricular failure and it became obvious that he required more adequate relief of the subvalvar aortic obstruction. The abnormal mitral subvalvar apparatus that was causing the obstruction was removed one week later during an elective procedure. On this occasion all the obstructing tissue was excised and the mitral valve and subvalvar apparatus were replaced with a 23 mm St Jude bileaflet mechanical prosthesis that was easily inserted (fig 2). The outflow tract gradient was reduced to 30 mm Hg.

The immediate postoperative course was uneventful and signs of heart failure soon disappeared. Good opening and closing sounds of the mitral valve were noted as were signs of mild aortic stenosis. Satisfactory anticoagulant control was achieved with warfarin. Two years later the child is well grown, vigorous, and symptom free. A recent cross sectional echocardiogram shows a normal sized

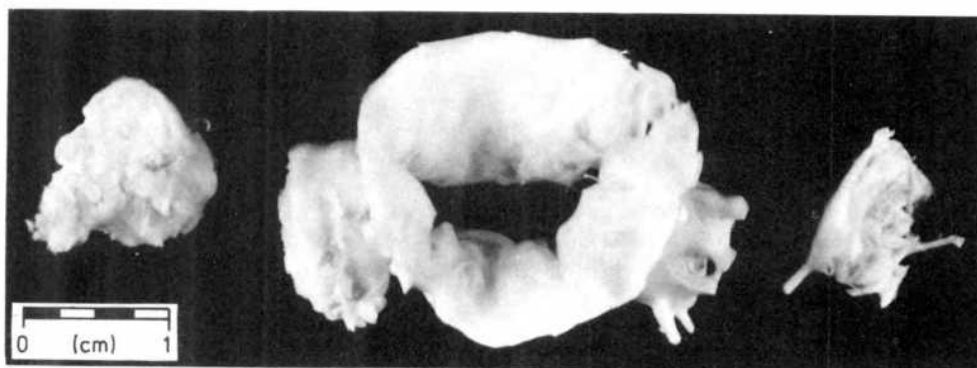


Fig 2 Excised mitral valve showing abnormal subvalvar apparatus and obstructive fibrous tissue.

left atrium, a mildly hypertrophied left ventricle that is contracting well, a bicuspid aortic valve, and a well seated prosthetic valve. A Doppler study confirmed the absence of paravalvar leak of the prosthetic valve and the presence of mild aortic stenosis and regurgitation. The electrocardiogram shows considerable reduction in left ventricular forces, and the chest radiograph shows a pronounced reduction in heart size. There have been no problems with anticoagulant control; his present regimen is warfarin 2 mg and 2.5 mg on alternate days.

Discussion

Anatomical abnormalities of the mitral valve and its subvalvar apparatus are well described.²⁻⁴ Anomalous mitral arcade causing mitral regurgitation because the papillary muscles are inserted directly into the leaflets or by short chordae tendineae was described by Laymon and Edwards.⁵ Subaortic stenosis has been reported in association with the abnormal basal insertion of the anterior mitral leaflet.⁶ In addition, it may occur as a result of accessory valve tissue, restriction of anterior cusp movement by accessory chordae tendineae, or abnormal attachment of valve tissue to the septal wall of the outflow tract.^{2,7,8} In our patient the sheets of fibrous subvalvar apparatus obstructed the left ventricular outflow tract and restricted anterior cusp movement in systole, thus causing mitral regurgitation.

Despite the necropsy evidence of subaortic stenosis associated with structural faults of the mitral valve and its apparatus there are few clinical reports of the condition. In this baby the striking clinical features were those of mitral incompetence, and left ventricular outflow tract obstruction was not definitely diagnosed until cardiac catheterisation. In retrospect, there is no doubt that there was a loud systolic murmur radiating to the neck and considerable left ventricular mid-cavity narrowing evident both on the cross sectional echocardiogram and on the left ventricular cineangiogram.

Others have reviewed mitral valve replacement in infants and children.⁹⁻¹¹ Few successful operations have been reported on infants aged <6 months. Selection of the appropriate prosthesis will increase the interval before replacement is needed.¹² The durability of cardiac bioprostheses is severely restricted by calcification and degeneration in infancy and childhood and for this reason we chose an artificial prosthetic valve for this infant.¹³⁻¹⁵ To postpone the development of stenosis of the prosthetic valve we chose a device with good orifice area to external diameter ratio; a low profile centrally opening prosthesis is probably most suitable for the mitral position.^{16,17} We therefore chose the St Jude

bi-leaflet prosthesis and implanted a valve with an external diameter of 23 mm and an orifice area for flow of 2.55 cm. Although the mean native adult mitral valve area is 8.2 cm, we hope that the implanted prosthesis will last for at least 10 years.

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Truncus arteriosus: successful surgical correction without the use of a valved conduit

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SUMMARY A new operation for the restoration of continuity between the right ventricle and pulmonary circulation in truncus arteriosus in infancy without the use of a tube graft is described. This was achieved by anastomosing the inferior margin of the detached confluent branch pulmonary arteries to the apex of a vertical infundibular ventriculotomy to form the posterior wall of the reconstructed right ventricular outflow tract. A patch of pericardium was used to form the anterior wall and complete the primary cardiac repair.

The surgical management of the infant with truncus arteriosus remains a challenge, although recent reports have indicated satisfactory results of corrective surgery in patients under one year of age.^{1,2} Major centres, however, still report high operative risks in small infants.³ The principles of repair and of intraoperative and postoperative management are becoming increasingly clear in this complex condition but invariably reports advise the placement of an appropriately sized Rastelli conduit, valved or otherwise, between the right ventricle and pulmonary arteries and accept the need for reoperation and further reconstruction at a later date.^{1,2,4} All conduits are liable to progressive stenosis, endocarditis, and valve failure if a valved conduit is used; reoperation carries its own important risk.^{5,6} Even if a second operation for conduit replacement is successful, it remains likely that a considerable number of children will require further operation especially after ten years with such a conduit.⁷

The preliminary work of Bailey *et al*⁸ has led us to devise an operative technique that obviates the need for conduit placement in the common types of truncus arteriosus, allows for potential growth, and seems to have important advantages over conventional techniques while still retaining the advantages of anatomical correction. We have used this technique to correct truncus arteriosus in an infant weighing 3 kg.

Case report

A 10 week old infant was referred to the Royal Hospital for Sick Children, Edinburgh with a history of failure to thrive and recurrent chest infections. She was tachypnoeic with a respiratory rate of 75 per minute, there was intercostal indrawing, the peripheral pulses were all of full volume with a collapsing quality, and the blood pressure in the right arm was 100/30 mm Hg. On auscultation both heart sounds were single and there was a long, harsh grade 4/6 systolic murmur and a grade 3/6 early diastolic murmur that were both loudest at the lower left sternal edge. A chest x ray showed cardiomegaly with a cardiothoracic ratio of 65% and increased pulmonary vascularity. Electrocardiographic examination showed biventricular hypertrophy with ST-T changes in the left lateral precordial leads.

The clinical features suggested a diagnosis of truncus arteriosus and this was confirmed on cardiac ultrasound examination which was interpreted as being in keeping with a type 1 truncus arteriosus and truncal valve regurgitation. After 48 hours of medical support and treatment with sedation, digoxin, frusemide, and ventilation she was taken to the operating theatre for repair of the defect.

OPERATIVE PROCEDURE

Figure 1a shows the anatomy of the vessels. There was no main pulmonary artery, both the right and left pulmonary arteries arose from the left lateral margin of the aortic root, the right artery being inferior in position and passing below the left vessel. Both arteries were extensively mobilised into both hila. The infant was cooled to 20-21°C while on

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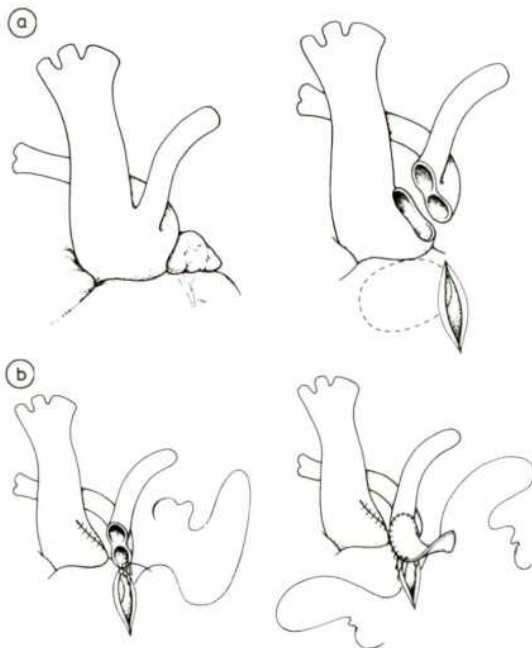


Fig 1 Diagrams showing restoration of continuity between the right ventricle and pulmonary circulation. (For details see text.)

cardiopulmonary bypass; the pulmonary vessels were gently clamped to avoid bypass perfusion of the lungs and they were resected from the aorta. Then a cannula was manipulated into the left coronary ostium and cardioplegia was continued. A superior

right ventriculotomy was made and through it the ventricular septal defect was closed. The aortotomy was repaired. The inferior margin of the right pulmonary artery was sewn to the superior margin of the ventriculotomy by means of a continuous to and fro Prolene suture. This suture was carried around one half of the inferior circumference of the right pulmonary artery opening, bringing it down on to the upper one quarter to one third of the ventriculotomy margin (fig 1b). The anterior defect thus created was closed with a carefully tailored patch of xenograft bovine pericardium (Shiley Corporation). The procedure established generous egress from the right ventricle.

POSTOPERATIVE COURSE

The infant's postoperative course was uneventful. She was extubated 48 hours after operation and required no inotropic support. Postoperatively there was a residual grade 2/6 to 3/6 early diastolic murmur. Fifteen days after operation cardiac catheterisation was performed. The right ventricular systolic pressure was 55 mm Hg and the pulmonary artery systolic pressure was 35 mm Hg, and a left ventricular peak systolic pressure was 90 mm Hg. Oximetry demonstrated a small residual left to right shunt of 1.5:1. There was no pressure difference across the left ventricular outflow tract. A selective right ventricular angiogram demonstrated free egress of contrast into the pulmonary arteries with no important narrowing or obstruction (fig 2). Left ventricular angiography showed a small residual ventricular septal defect at the lower margin of the

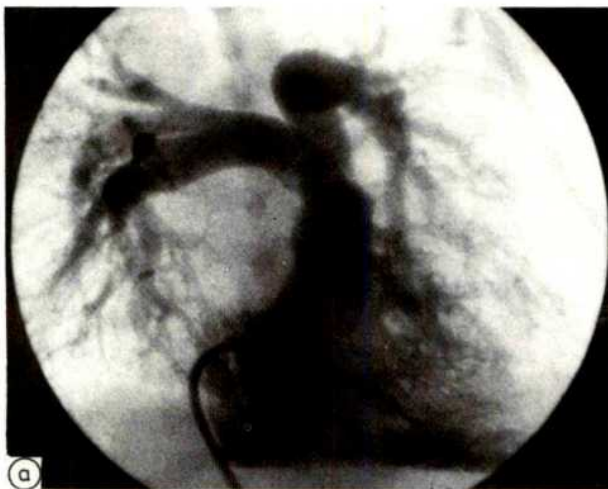


Fig 2 Postoperative right ventricular angiogram (anteroposterior and lateral views) demonstrating free egress of contrast into the pulmonary arteries with no important narrowing or obstruction.



ventricular septal patch that had been inserted at operation. On aortography there was a mild to moderate degree of aortic valvar regurgitation.

Discussion

Orthodox right ventricular outflow tract reconstruction for other types of congenital heart disease is accomplished by transannular patching with pericardium or preclotted Dacron and follow up studies show an apparently normal propensity for growth. What is less certain is the efficacy of the valve leaflets and whether they are necessary for medium and long term success since adult cases can be symptom free in the face of chronic pulmonary valvar incompetence which, while not necessarily benign, is well tolerated.⁹ Our experience with this case agrees with that of others who have used non-valved conduits in this condition; we cannot agree with Bailey's conclusion that a competent pulmonary valve is required for short term survival. Moreover, the development in Bailey's case of a right ventricular outflow tract aneurysm within 40 days is strongly suggestive of important residual right ventricular hypertension that could have contributed to early death.

There are practical and theoretical advantages in applying this technique of right ventricular outflow tract reconstruction to types I and II truncus arteriosus. These include (a) ease of operation, (b) growth potential of the right ventricular/pulmonary artery junction, and (c) avoidance of the acknowledged severe early and late complications of conduit placement in very young infants. We acknowledge the persistence of the native truncal valve regurgitation and the possibility that this could worsen with time.

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Failure of Quintech Tx pacemaker caused by loss of stimulus-T interval shortening during exercise

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SUMMARY A 74 year old man with a Quintech Tx pacemaker experienced a reduction in his exercise capacity because his heart rate failed to increase with effort. This was shown to be caused by the failure of the interval between the delivered stimulus and evoked T wave to decrease during effort where previously it had done so. Although the stimulus-T interval did not change during exercise, it did decrease in response to isoprenaline infusion and in response to pacing the heart at increasing rates. Catecholamine concentrations increased during exercise and the patient had normal thyroid function.

Pacemakers which increase the heart rate during exercise have been shown to improve exercise tolerance,¹ and sensing of the stimulus-T interval shortening that occurs during exercise is one method by which this can be achieved.² A patient is described who experienced a reduction in his exercise capacity because his Quintech Tx pacemaker failed to increase his heart rate during exercise; this was apparently because the interval between the delivered stimulus and evoked T wave did not shorten.

Case report

The patient, who had had a mitral valve replacement in 1971 at the age of 60, had a Quintech Tx pacemaker implanted in January 1983 at the National Heart Hospital because he had four syncopal attacks during exercise and had also experienced dizziness during exercise. He was in atrial fibrillation with a resting heart rate around 50-60 beats/min with asymptomatic ventricular pauses of 2-4 s. On exercise testing his ventricular rate did not exceed 80 beats/min and his systolic blood pressure fell from 180-190 mm Hg to around 120 mm Hg by the latter half of the first stage of the Bruce protocol. At

implantation the pacemaker did not sense T waves because of their low amplitude but one month afterwards, exercise testing showed that the pacemaker was working satisfactorily and achieving paced heart rate during effort of 125 beats/min associated with an interval of 0.44 s between the delivered stimulus and evoked T wave. Eight months later (September 1983) he had three blackouts when exercising and noticed giddiness during exercise and on rising from a chair.

Testing subsequently showed that he was having ventricular extrasystoles during exercise which were thought to be interfering with pacemaker function. The system was adjusted and his exercise tolerance improved from stage I to stage III of the Bruce protocol on treadmill testing. The pacemaker increased his heart rate to 140 beats/min during exercise. His exercise capacity again deteriorated and exercise testing in October 1985 showed that the stimulus-T interval recorded on the surface electrocardiogram

Table 1 *Plasma noradrenaline and adrenaline concentrations before and after exercise to 1 min into the second stage of the Bruce protocol*

	Resting	End of exercise	5 min after exercise
Noradrenaline (nmol/l)	1.46	3.00	1.72
Adrenaline (nmol/l)	0.94	2.29	1.18

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Table 2 *Effect of intravenous isoprenaline infusion on pacemaker rate and the stimulus-T interval recorded on the surface electrocardiogram*

	Infusion rate											
	1 $\mu\text{g}/\text{min}$						2 $\mu\text{g}/\text{min}$					
Time (min)	0	1	2	3	4	5	6	7	8	9	10	11
Pacemaker rate (per minute)	71	71	71	75	75	75	75	75	100	130	130	130
Stimulus-T interval (s)	0.48	0.48	0.48	0.48	0.48	0.48	0.48	0.48	0.44	0.42	0.40	0.42

Table 3 *Effect of increasing rates of pacing on the stimulus-T interval recorded on the surface electrocardiogram*

Rate of ventricular pacing/min	80	90	100	120	130
Stimulus-T interval (s)	0.48	0.44	0.44	0.42	0.40

by means of a Marquette triple channel machine at a paper speed of 50 mm/s remained static at 0.48 s during exercise up to 1 min into stage II of the Bruce protocol and during recovery. The rhythm throughout was ventricular pacing at 71 beats/min. Table 1 shows that plasma adrenaline and noradrenaline concentrations were normal at rest and that the increase in noradrenaline concentration during exercise was also normal. The increase in adrenaline concentration was somewhat higher than expected but was not unreasonable for the conditions of extra stress of the test.

Isoprenaline was then infused intravenously at a rate of 1 $\mu\text{g}/\text{min}$ for 5 min, followed by 2 $\mu\text{g}/\text{min}$ for 3 min. It was stopped when occasional non-paced beats appeared. Table 2 shows that the stimulus-T interval shortened in response to isoprenaline and that the pacemaker sensed this and increased its rate. The increase in pacing rate from 71 to 75 beats/min without apparent shortening of the stimulus-T interval is probably the result of slight shortening of the stimulus-T interval that was sensed intracardiacally by the pacemaker but was not apparent on the surface electrocardiogram.

Because the pacemaker did not increase the patient's heart rate during exercise it was replaced with a Medtronic Activitrax pacemaker which increases its rate by sensing increasing skeletal muscle noise during exercise. This improved his exercise tolerance and enabled him to exercise to 1 min into stage III of the Bruce protocol. At the time of implantation we paced the ventricle via the existing Quintech lead at various rates. The surface stimulus-T interval shortened with increasing rates of pacing as shown in table 3.

There was non-specific anaemia (haemoglobin 11 g/dl) and the blood urea concentration was marginally raised (7.9 mmol/l, normal upper limit 7.5 mmol/l). The following investigations were normal—plasma thyroxine and thyroid stimulating

hormone; serum sodium, chloride, calcium, and phosphate concentrations; liver function tests; Synacthen test (tetracosactrin); and urinary metadrenalines. The only drug that he was taking regularly was Moduretic (amiloride hydrochloride and hydrochlorothiazide).

Discussion

This patient's Quintech Tx pacemaker lost its capacity to increase its rate with effort because the patient's stimulus-T interval failed to shorten. We showed that the stimulus-T interval did shorten in response to isoprenaline infusion and that the pacemaker was capable of sensing this and increasing the heart rate. The pacemaker, therefore, was capable of functioning normally.

Catecholamine release is known to be important in causing shortening of the stimulus-T interval during exercise³ but the possibility that the failure of the stimulus-T interval to shorten might be due to failure of catecholamine release has been excluded. Because the stimulus-T interval did not decrease during exercise despite an adequate rise in catecholamine concentrations, the obvious conclusion is that the heart had become less sensitive to catecholamines. We have excluded the commonest cause of catecholamine resistance which is hypothyroidism. The reason that the stimulus-T interval did not decrease during exercise remains a mystery.

According to the manufacturers (J H Gray, personal communication) there has been only one other case in over 2000 implants of this type of pacemaker in which there was no change in the QT interval during exercise. This abnormality is difficult to recognise before pacemaker implantation, however, because the QT interval still changes in response to changes in heart rate per se (as it did in our patient when pacing rates were increased) and therefore the problem can only be recognised when the heart rate

can be held constant during exercise. In order that the failure is not misdiagnosed as a pacemaker sensing problem it is important that this abnormality should be looked for in all cases where a Tx pacemaker fails to increase its rate during exercise.

We thank Professor J Reid, Stobhill Hospital, Glasgow, for measuring noradrenaline and adrenaline concentrations.

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Correspondence

Radiation hazards for cardiologists

Sir,

The Editorial by Raphael and Tomlinson (1986;55:421-2) was an interesting review of some specific aspects of radiation dosage to cardiologists. The authors advised, quite correctly, that those performing catheterisations should be instructed in radiation safety practice before or early in their training. They did not point out, however, the complete absence of structured tuition in radiation physics and radiation protection for cardiology trainees.

A trainee radiologist in his first year of training must attend a formal course of instruction in radiation physics (including radiation protection) and must pass an examination (Fellowship of the Royal College of Radiologists part I) before being allowed to continue and complete his or her training as a radiologist. Similarly, a student radiographer must undergo full formal training and examination before being allowed to expose a single radiograph without supervision.

In sharp contrast with this, most cardiologists in the United Kingdom perform cardiac angiography without any formal training or an examination.

While the clinical skills of cardiology are probably best learned informally during the course of clinical

duties, the same cannot be said for the study of radiation physics; particularly when seniors are usually also untrained.

The subject of radiation exposure is especially topical and cardiologists will leave themselves increasingly open to criticism if they continue their close involvement with ionising radiation without taking sensible action to institute proper training. The imminent Euratom directive from the European Economic Community may well make such training a legal necessity.

A final related point is that the radiologist learns radiation physics not only to protect himself and others but also to ensure optimal function of equipment and thus optimal diagnostic accuracy. If a cardiologist without such training works in an institution which also has no integrated cardiac radiological involvement (as happens in many centres) it is a matter for speculation as to how adequate standards of equipment operation and angiographic quality are maintained.

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Notices

British Cardiac Society

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 25 to 27 November 1986, and the closing date for receipt of abstracts was 11 July 1986.

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Editorial: twenty years of prehospital coronary care <i>J S Geddes</i>	491	Effects of verapamil on haemodynamic function and myocardial metabolism in patients with hypertrophic cardiomyopathy <i>P T Wilmshurst, D S Thompson, S M Juul, B S Jenkins, M M Webb-Peploe</i>	544
Smoking: a major predictor of left ventricular function after occlusion of the left anterior descending coronary artery <i>W B McKenzie, R M McCredie, C A McGilchrist, D E L Wilcken</i>	496	Left atrial myxoma: new perspectives in the diagnosis of murmur free cases <i>P Nihoyannopoulos, P Venkatesan, J David, D Hackett, H Valentine, C M Oakley</i>	554
Morphological characteristics of clinically significant coronary artery stenosis in stable angina <i>J R W Hangartner, A J Charleston, M J Davies, A C Thomas</i>	501	Case reports Infective endocarditis affecting the eustachian valve <i>A D Edwards, M A Vickers, C J Morgan</i>	561
Effect of the specific thromboxane receptor blocking drug AH23848 in patients with angina pectoris <i>D P De Bono, P Lumley, M Been, R Keery, S E Ince, D F Woodings</i>	509	Staged septation of double inlet left ventricle <i>R McKay, R M Bini, J P Wright</i>	563
The haemodynamic response to myocardial ischaemia in ambulant patients with variant angina <i>R D Levy, L M Shapiro, C Wright, L J Mockus, K M Fox</i>	518	Coincidence of true and false left ventricular aneurysms after myocardial infarction <i>M Coupe, M Dancy, J Pepper</i>	567
The haemodynamic significance of asymptomatic ST segment depression assessed by ambulatory pulmonary artery pressure monitoring <i>R D Levy, L M Shapiro, C Wright, L J Mockus, K M Fox</i>	526	Abnormal diastolic movement of the interventricular septum caused by a prolapsing right atrial myxoma <i>D R Ramsdale, G J Green, R G Charles</i>	569
Mechanism of the dicrotic pulse <i>D Smith, E Craige</i>	531	Fatal heart block due to mesothelioma of the atrioventricular node <i>D W Evans, P G I Stovin</i>	572
Tricuspid atresia in adolescents and adults: current state and late complications <i>C A Warnes, J Somerville</i>	535	Correspondence	575
		Notices	576
		Validation of a study	576
		Index	577

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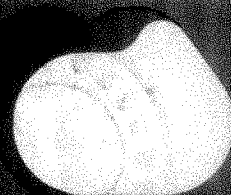
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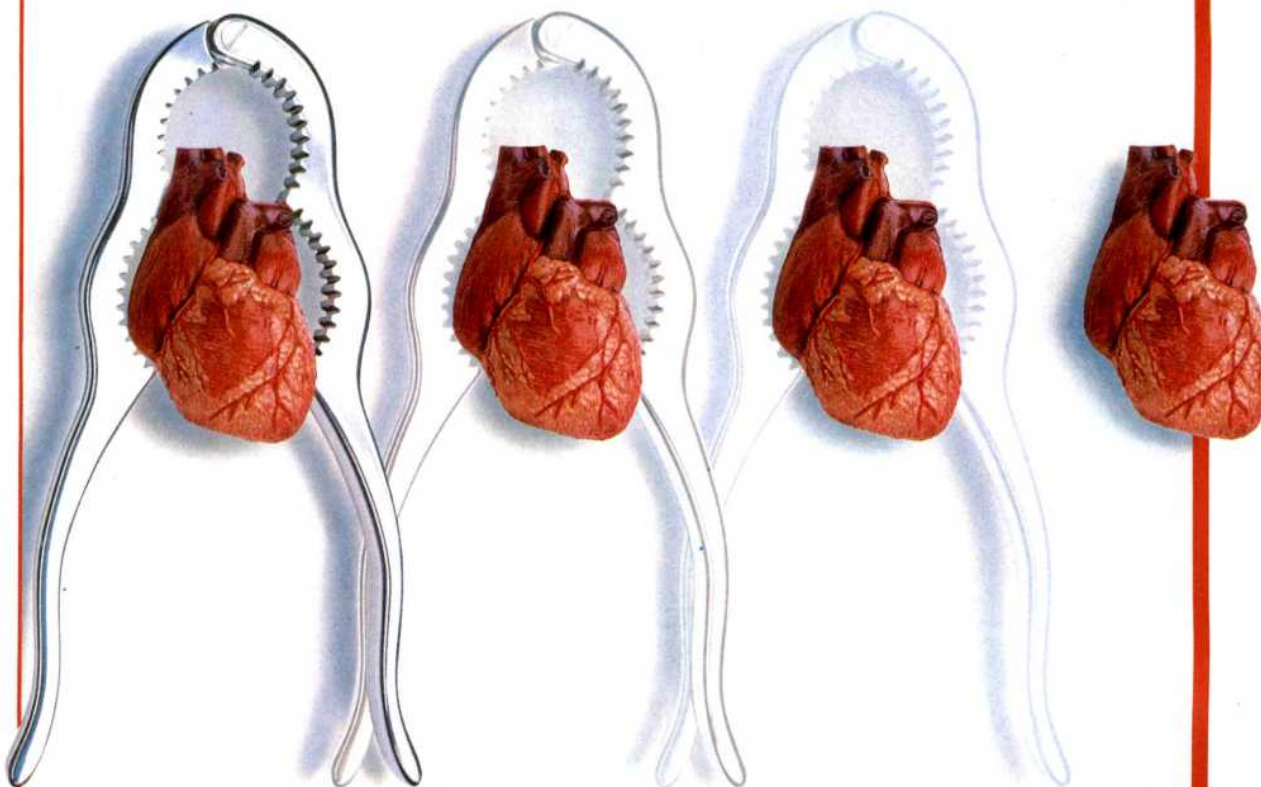
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Editorial

Twenty years of prehospital coronary care

J S GEDDES

From the Cardiac Department, Royal Victoria Hospital, Belfast, Northern Ireland

By 1965 the possibility of preventing deaths from arrhythmia among those stricken with coronary attacks was already well established. The realisation that most of these deaths occur shortly after onset and therefore outside hospital led to the recognition that hospital coronary care units were of limited value because most patients who reached them were already either convalescent or moribund. Professor JF Pantridge (then Dr) and I therefore decided to arrange that trained staff with equipment should reach the coronary victim as soon as possible after the onset of the attack. A mobile coronary care unit was introduced in Belfast on 1 January 1966.¹ At that time the components had to be assembled to make a defibrillation system available.

We soon demonstrated that resuscitation from ventricular fibrillation could be achieved in the pre-hospital setting.^{2,3} The system was successful in reaching the majority of patients early and this reduced the disparity in place and time between the need for coronary care facilities and their availability. Furthermore, deaths during transport to hospital were virtually eliminated among patients receiving prehospital care.

During the subsequent years prehospital coronary care systems were established in many parts of the world.⁴ Some of these units were staffed by physicians but, particularly in the United States, the tendency grew for staffing to be provided by paramedical workers, technicians, or a tiered combination of both. In Britain a unit staffed by specially trained ambulancemen was set up in Brighton in 1971.⁵ Against the background of these developments it is useful, after two decades, to survey the achievements of prehospital systems and to consider why the principle has been accepted with enthusiasm in some countries and not in others.

As experience of the acute phase of infarction in

Belfast increased it became apparent that early management had beneficial effects extending far beyond the prompt relief of pain and the correction of ventricular fibrillation at the place of onset or during transit. Some life threatening arrhythmias may have been prevented by the use of antiarrhythmic drugs and many episodes of ventricular fibrillation were corrected in hospital before the patients would normally have come under intensive care. Of perhaps even greater importance were the manifestations of autonomic disturbance that were commonly present during the early hours of infarction and which could undoubtedly trigger ventricular fibrillation.⁶⁻⁸ Among patients seen within 30 minutes, one half had evidence of vagal overactivity (almost half of these had systolic blood pressure of ≤ 80 mm Hg) and a third had evidence of inappropriate sympathetic discharge. Combined autonomic disturbance was not uncommon.

Correction of the acute disturbances conferred unexpected benefits. Among patients aged 70 or less seen and treated within the first hour, hospital morbidity was only 9% and cardiogenic shock was rare. Pantridge's hypothesis, in 1970, that early treatment by permitting the correction of adverse abnormalities of heart rate and blood pressure might prevent unnecessary extension of the infarct⁹ led to much interest in the limitation of infarct size, an interest which continues.

Mechanisms of the beneficial effect of early care

Insufficient attention has been paid to the two distinct mechanisms by which early prehospital care can reduce morbidity and mortality. Although the skills of trained ambulancemen and paramedical workers should not be underestimated, the unit manned by non-physicians seems to have more to contribute to resuscitation than to the correction of disturbances of rate, rhythm, and blood pressure, a

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process which often requires titration with atropine, β blocking drugs, or antiarrhythmic agents to avoid the vicious cycle of inexorable extension of the infarct and increasing pump failure.

RESUSCITATION

The lessons learned in the hospital coronary care unit have been echoed by development of facilities for out of hospital correction of ventricular fibrillation, notably in Seattle, where a prehospital system was started in 1970.¹⁰ Emergency medical technicians (firemen), who are widely dispersed in the community, take an average of three minutes to reach a patient. They provide basic life support until paramedical workers arrive a few minutes later.

The baseline survival rate for this approach was about 20%.¹¹ With the addition of refinements salvage was greatly increased. Immediate cardiopulmonary resuscitation by trained bystander members of the public doubled the percentage of survivors¹²; when the delay in defibrillation was also short, 50% survival was achieved.¹³ Similar results were obtained when subsequently the first responders were able to defibrillate without waiting for arrival of the paramedical workers.¹⁴ The potential survival rate under ideal conditions in which a defibrillator is available to the person activating the emergency system is estimated to be as high as 70%.¹⁵ Neurological recovery and long term health status were generally better when resuscitation and defibrillation had not been delayed.^{14 16}

The benefits vary according to local circumstances.¹⁷ Nevertheless, the advantages of streamlining cardiopulmonary resuscitation, definitive care, or both have been confirmed in other parts of the United States¹⁷⁻¹⁹ and in Britain²⁰ and Sweden.²¹

LIMITATION OF INFARCT SIZE

Units manned by physicians excel at the prehospital stabilisation of patients with suspected acute infarction. Economic considerations dictate that these units cannot be so numerous or so widely distributed as those staffed by paramedical workers; nevertheless, many patients with ventricular fibrillation have been resuscitated by such units.^{22 23} Equally important has been the confirmation elsewhere²³ of the Belfast finding²² that the outlook of patients treated early is better than that of those seen later after onset. In addition, community mortality among persons below age 70 fell when prehospital care was introduced in Charlottesville, Virginia, and not all of the observed reduction could be ascribed to resuscitation.²⁴

Resuscitation results in a readily identifiable salvage but the specific effects of the early treatment

of infarction in preventing life threatening arrhythmia and extension of myocardial necrosis are less easily quantified. Recent evidence supports the view that these effects are substantial.²⁵ Community mortality from coronary attacks was surveyed in two comparable areas of Northern Ireland. One area had prehospital coronary care and the other had a hospital coronary care unit only. Mortality in the area with a mobile unit was significantly less than that in the other area and the difference was conspicuous in the younger age groups. Among persons aged <65 community mortality was 38% lower, and this difference was not attributable to prehospital resuscitation.

THE NOTTINGHAM STUDIES

Earlier attempts at the evaluation of the possible impact of prehospital care in Nottingham yielded disappointing results,²⁶⁻²⁸ and undoubtedly these, together with the result of the Bristol study of home versus hospital treatment of myocardial infarction,²⁹ delayed the recognition of the value of prehospital care in Britain. The absence of an appreciable reduction in mortality in Nottingham was ascribed to difficulties in arranging for the unit to reach many patients while it was possible to alter the course of their coronary attacks.³⁰ The Nottingham workers largely based their criticism of the relevance of the Belfast data on the finding that surviving patients seen by the Nottingham mobile unit belonged to a low risk group. They apparently considered that the low mortality among patients managed during the prehospital phase elsewhere was the result of similar selection of low risk patients. But they overlooked the fact that the relevant evidence supporting the value of prehospital care was derived from a comparison of the outcome for patients seen and treated early with that for patients first seen after a longer delay.^{22 23}

The studies performed by the Nottingham workers gave an invaluable insight into the difficulties inherent in initiating an effective prehospital service. It is unfortunate that their results began to appear immediately after the publication in 1975 of the recommendations of the Joint Working Party of the Royal College of Physicians and the British Cardiac Society on the care of the patient with coronary heart disease.³¹ The Department of Health and Social Security did not, as recommended in the working party report, encourage the development of mobile coronary care but rather placed an embargo on the extension of schemes of advanced training for ambulancemen.³² Had the recommendations of the working party on the further development of prehospital care (the exact means depending on local conditions and requirements), on the instruction of

the public in resuscitation, and on the importance and means of summoning help quickly been received by the Department of Health and Social Security with the enthusiasm and flexibility of approach envisaged in their report, there can now be no doubt that very many lives would have been saved during the intervening decade.

The portable defibrillator

The "portable" defibrillation system carried in the first mobile unit in Belfast weighed 50 kg. Clearly the wide proliferation of prehospital schemes would have been impossible but for the advent of more easily portable machines. In 1974 a miniature defibrillator weighing only 3.2 kg appeared.³³ The waveform of 12 ms duration delivered by this machine had been found by Peleska to be optimal for defibrillation of laboratory animals.³⁴

A signpost to possible further miniaturisation was the observation by the Belfast workers that a stored energy of only 200 J is sufficient to defibrillate the hearts of 95% of patients.³⁵ The efficacy of low energy levels was confirmed by others.^{36,37} Repeated shocks of 400 J stored energy cause myocardial damage in animals.³⁸ Shocks of this magnitude, which are usually not necessary clinically, may cause functional disturbance in man.³⁷

Because the ease with which delay of defibrillation in the community may be avoided will be inversely proportional to the size, weight, and cost of defibrillators, the availability of a low energy machine could contribute to the survival of many more patients. Because of their additional bulk and uncertainty about the adequacy of rhythm interpretation, combined defibrillator/oscilloscopes will be of limited value for use by first responders. The long awaited miniaturised automatic external defibrillator is already undergoing clinical evaluation.^{39,40} If minimally trained technicians or family members of those at risk could use these machines, the delay inherent in awaiting the arrival of more skilled help would be avoided. Domiciliary defibrillation facilities must increase because many of the survivors of prehospital cardiac arrest will be at considerable risk of recurrence.

The future of prehospital coronary care

Fortunately, the Department of Health and Social Security has decided to encourage the development of prehospital care through the extended training of ambulancemen. In addition, a unique programme of instruction of the general public in basic life support via the media, known as the "Save a Life Campaign," is just beginning under the auspices of the

Royal Society of Medicine. These developments when fully implemented will undoubtedly prevent many deaths from arrhythmia after acute coronary attacks. Even in Belfast, which is served by two mobile units, in a one year period 128 sudden and premature prehospital deaths were identified. Many might have been prevented by immediate appropriate action by someone present at the time.⁴¹ An estimate based mainly on data from Auckland indicates that prehospital resuscitation appears to have made the greatest single contribution (40%), attributable to medical measures, to the reduction in coronary mortality yet the incidence of sudden death there has fallen by only 16%.⁴²

The energetic application of public education programmes in cardiopulmonary resuscitation of the type already devised in Britain⁴³ and the United States⁴⁴ is required. Such education should be especially aimed at those most likely to witness a cardiac arrest,⁴⁵ such as families of middle aged men and of others known to be at special risk. Because even moderately efficient resuscitation may suffice during the first few minutes before the arrival of advanced life support, it may be rewarding to devise and teach a simplified technique for use by the "occasional bystander".

Will a nationwide prehospital system based mainly on the emergency ambulance service, as envisaged by the Department of Health and Social Security, be sufficient to meet present and future needs? Can ambulancemen give drugs to limit infarct size? As emphasis is increasingly placed on the prevention rather than the limitation of infarction, the need for the administration of thrombolytic agents will increase.⁴⁶ Perhaps hospitals could give guidance on the telephone in such circumstances. For the present, however, these needs can best be met in Britain by using doctors on the teams. In the best prehospital system an ultrarapid emergency ambulance tier (several vehicles) would be supported by a hospital tier (one or two teams) resembling the prehospital scheme started in Charlottesville in 1971.²⁴ Such a system will shortly come into operation in Ballymena as an extension of a well established medically manned mobile unit (C Wilson, personal communication).

Comprehensive coverage of city and rural areas will require considerable ingenuity and it is here that organisations such as the British Association for Immediate Care and the Association of Emergency Medical Technicians will play an increasingly important coordinating role. In rural areas the general practitioner can often reach the stricken individual first. Defibrillation by general practitioners has been shown to be highly rewarding.⁴⁷ Delineation of the responsibilities of the family doctors and of the

emergency ambulance service in each area could result in worthwhile economies.

The proficiency of hospital doctors in basic and advanced life support must keep pace with the progress being made by citizens and paramedical workers. When the cardiopulmonary resuscitation skills of junior medical hospital staff were tested in some hospitals in Britain and the United States the results were disappointing.⁴⁸⁻⁵⁰ Medical schools and physicians in related specialties must ensure that public education and training are paralleled by adequate teaching of the necessary skills at undergraduate and postgraduate levels.

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Smoking: a major predictor of left ventricular function after occlusion of the left anterior descending coronary artery

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SUMMARY The major predictors of left ventricular function after coronary artery occlusion were assessed in 108 consecutive patients who had complete occlusion of the left anterior descending artery as the only important lesion demonstrated at angiography between June 1978 and June 1983. A scoring system was used to identify regional damage on left ventriculograms. Forty two patients were classified as having good left ventricular function and 66 as having varying degrees of impairment. Apart from a history of myocardial infarction, the only variables discriminating between those with good and those with impaired left ventricular function were the area of distribution of the artery beyond the occlusion and cigarette smoking. Hypertension, hypercholesterolaemia, family history of vascular disease, diabetes, obesity, duration of angina, age, and presence of identifiable collaterals were not discriminators. Smoking was itself significantly associated with a history of infarction; but after controlling for this, smoking exerted a significant additional effect on the amount of left ventricular damage.

It is concluded that smoking is not only a risk factor for myocardial infarction in patients with single left anterior descending artery occlusion, but that it is also a major factor in determining the extent of associated left ventricular damage.

Disease of a single coronary artery may cause little change in ventricular function in some patients and severe impairment or aneurysm formation in others.¹ It is important to identify the factors responsible for these differences, because ventricular function is the principal determinant of outcome in patients with ischaemic heart disease.^{1,2}

To assess the influence of various angiographic and clinical factors on the amount of left ventricular dysfunction after occlusion of a single major coronary artery, we studied 108 consecutive patients in whom complete occlusion of the left anterior descending coronary artery was the only important luminal obstruction found at coronary angiography.

Patients and methods

One hundred and eight consecutive patients with isolated left anterior descending occlusion were identified from the 2150 patients who underwent coronary arteriography in our laboratory between June 1978 and June 1983. All patients had complete occlusion of the left anterior descending coronary artery, with no important (> 50% diameter) stenoses in the circumflex or right coronary arteries. In all patients the left ventriculogram was technically adequate for assessment of regional wall motion.

The severity of left ventricular dysfunction and of coronary artery disease was assessed in each patient by the scoring system devised by Brandt *et al.*³ Representative systolic and diastolic frames from the 45° right anterior oblique left ventriculogram were traced and the ventricular outline in diastole was divided into five segments: the anterobasal, anterolateral, apical, diaphragmatic, and posterobasal. Depending on its systolic wall motion, each segment

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was given a numerical value (normal = 0, hypokinetic = 1, akinetic = 2, dyskinetic = 3), and the scores of the five individual segments were summed to arrive at an overall left ventricular score. Patients with scores of 0–2 were arbitrarily classified as having “good” left ventricular function (group 1) and those with a score of 3 or more as having impaired left ventricular function (group 2).

Coronary arteriograms were performed in multiple views by the Sones’ or Judkins’ techniques. We used Brandt’s scoring system³ to give each stenosis of a major coronary artery a numerical value that depended upon its site (proximal or distal), its severity, and its area of supply. In this system, possible coronary scores range from 0 (if all arteries are normal) to 15 (if there is a total occlusion of all three coronary arteries).

Identifiable collateral vessels were graded according to the degree of opacification of the distal anterior descending artery seen during coronary angiography: zero if a distal vessel was not identified; 1 if the distal vessel was seen only faintly and incompletely; 2 if the distal vessel was completely opacified; and 3 if the distal segment was as well opacified as the vessel being injected. This assessment was made after both right and left coronary injections, the two values being summed to give a collateral score.

To determine the important predictors of left ventricular function after left anterior descending artery occlusion, we compared several pre-existing variables in the patients with good (group 1) or impaired (group 2) left ventricular function. These included smoking, hypertension, family history of premature vascular disease, serum cholesterol, diabetes, body mass index, and duration of angina, the latter indicating possible predisposition to collateral formation. We also assessed variables that presumably result from left anterior descending coronary artery occlusion—area of supply as reflected by coronary artery score, a history of infarction, and the presence of abnormal Q waves on the electrocardiogram.

Patients were classified according to smoking history at the time of infarction or first presentation as: non-smokers, patients who had not smoked for at least two years; and light smokers, those smoking <10 cigarettes a day and pipe and cigar smokers; moderate smokers, between 10 and 20 cigarettes daily; heavy smokers >20 cigarettes a day. A period of abstention of two years was chosen for non-smokers because data from the Framingham study, confirmed by Rosenberg *et al.*, showed that by this time the risk of a cardiovascular event reverted to that found in people who had never smoked.^{4,5}

Patients with a blood pressure >150 mm Hg systolic or >95 mm Hg diastolic or who had been

treated for hypertension were regarded as having hypertension. Patients were classified as having a family history of ischaemic heart disease if ischaemic heart disease had developed in a first degree relative aged <60. Fasting serum cholesterol, height, weight, and body mass index were measured at the time of cardiac catheterisation.

We performed stepwise discriminant analysis (*Statistical Package for the Social Sciences*) of the variables shown in table 1 to discriminate between group 1 (good left ventricular function) and group 2 (impaired left ventricular function) patients. This program shows variables that discriminate between the two groups and at each step in the analysis selects the variable that gives the best discrimination. A statistic which is used to evaluate a discriminating variable is termed “F to enter” and in this calculation any value >3.96 is significant at the 5% level. The same discriminant analysis was used when a history of infarction was included in the analysis.

Results

Of the 108 patients with isolated complete occlusion of the left anterior descending coronary artery, 90 were male (mean age 51 years, range 34–69 years) and 18 were female (mean age 51 years, range 34–63 years). Most had symptoms of angina (74), left ventricular failure (10), or arrhythmia (4) and were studied with a view to bypass surgery. Twenty were symptom free or had only slight symptoms; most of these were younger patients with a history of myocardial infarction or of atypical chest pain in whom angiography had been performed mainly as a guide to prognosis.

Ventricular function was normal (score of zero) in 22 patients and abnormal in 86. Figure 1 shows the distribution of ventricular scores among the 108 patients studied. Forty two patients had ventricular scores of 0–2 and were included in group 1 (“good” left ventricular function). The remaining 66 patients had ventricular scores of 3–9 and were included in group 2 (“impaired” left ventricular function). The cut off point of 0–2 for group 1 was chosen arbitrarily because the statistical significance of the results was not different if group 1 patients included only those with scores of 0–1 or was extended to include those with scores of 0–3.

Figure 2 shows the coronary artery scores in the 108 patients ranged from 3 to 9.

Stepwise discriminant analysis of the pre-existing variables in table 1 shows that only two, smoking ($p < 0.00005$) and left anterior descending coronary score ($p = 0.0005$) are significant discriminators. The program selects smoking classification as the

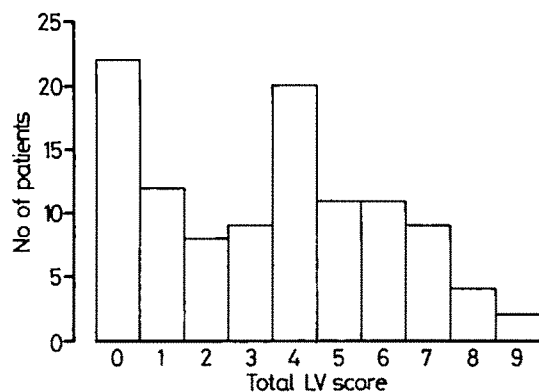


Fig 1 Distribution of left ventricular (LV) scores determined at left ventriculography in 108 consecutive patients with isolated complete occlusion of the left anterior descending coronary artery.

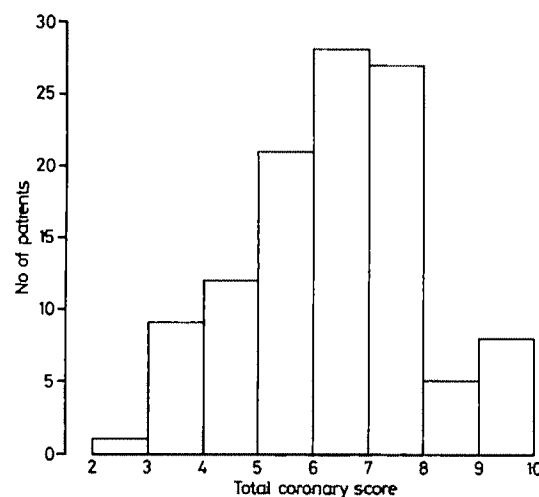


Fig 2 Distribution of coronary artery scores determined at coronary angiography in 108 consecutive patients with isolated complete occlusion of the left anterior descending coronary artery.

best discriminator. In group 1, 22 (52%) of 42 were non-smokers compared with 11 (17%) of 66 in group 2. After the coronary score is included the "F to enter" value of smoking remains relatively unaffected. Had there been a good association between the effects of these two variables on total left ventricular score, the fitting of one would have much reduced the "F to enter" of the other. There is, therefore, a largely separate effect of the two variables on left ventricular function as determined by total left ventricular score.

Table 2 shows the results when factors that presumably result from total left anterior coronary

Table 1 Stepwise discriminant analysis of pre-existing variables in 42 group 1 ("good" left ventricular function) and 66 group 2 ("impaired" left ventricular function) patients with isolated complete occlusion of the left anterior descending coronary artery

Variable	F to enter	
	Step 1	Step 2
Left anterior descending artery score	12.76**	—
Smoking	18.07*	16.50***
Hypertension	0.71	0.81
Cholesterol	0.53	0.36
Family history	0.01	0.07
Body mass index	0.05	0.30
Age	1.19	1.79
Duration of angina	1.91	0.49
Diabetes	0.10	0.05

Step 1, only smoking ($p < 0.00005$)* and left anterior descending artery score ($p = 0.0005$)** are significant discriminators.

Step 2, inclusion of left anterior descending artery score in the analysis has little effect on the "F to enter" value of smoking ($p < 0.0005$ ***).

Table 2 Stepwise discriminant analysis between group 1 and group 2 patients by history of infarction, abnormal Q waves in electrocardiograph, and collateral score

Variable	F to enter		
	Step 1	Step 2	Step 3
Infarct history	35.68*	—	—
Left anterior descending artery score	12.76	15.89	—
Smoking	13.64	8.52	7.20**
Collateral score	0.01	0.01	0.06
Q waves	1.18	1.21	0.91

Step 1, history of infarction is the most significant discriminator in those with impaired left ventricular function ($p < 0.00005$)*.

Step 2, inclusion of history of infarction and left anterior descending artery score in the analysis reduces the "F to enter" value of smoking, but it still remains significant ($p = 0.008$)**.

artery occlusion—history and electrocardiographic evidence of infarction and formation of angiographically visible collateral vessels—were included in the analysis. History of infarction is a significant discriminator ($p < 0.00005$) but not the presence of abnormal Q waves in the electrocardiogram ($p = 0.28$) or the formation of identifiable collateral vessels ($p = 0.91$). When history of infarction was included in the analysis, however, the "F to enter" value of smoking remained highly significant ($p = 0.008$); that is smoking remained an additional independent discriminator. Also discriminant analysis showed that smoking was significantly more common in those with a history of infarction ($p = 0.014$).

Discussion

In this group of patients in whom complete occlusion of the left anterior descending coronary artery was the only important lesion ventricular function ranged from normal to severely impaired. The differences presumably reflect variations in the incidence and extent of myocardial infarction. Of the variables analysed in an attempt to explain these differences, apart from a history of myocardial infarction, only the area of supply distal to the left anterior descending occlusion and history of cigarette smoking were of significance in discriminating between patients with good and impaired left ventricular function. Discriminant analysis established that these two variables were acting independently. This remained true if the cut off point for group 1 ("good" ventricular function) was taken at a ventricular score of 2 or 3, and even if the nine light smokers in this study were classified as smokers rather than non-smokers. Age, sex, family history of vascular disease, or abnormal Q waves in the electrocardiogram, collateral score, or the presence of other major risk factors for coronary artery disease did not discriminate between the two patient groups.

It is known that lesions of the left anterior descending artery at different sites are associated with differences in left ventricular function. Patients with stenoses of the proximal left anterior descending artery have greater depression of ejection fraction,⁶ more abnormal wall motion,⁷ and more profound exercise dysfunction⁸ than do similar patients with distal stenoses. Such findings are not unexpected because the quantity of myocardium dependent upon a major coronary artery decreases as flow progresses more distally in the vessel. The results of the present study accord with these findings.

Cigarette smoking is associated with more severe and extensive coronary atherosclerosis and smokers have a considerably increased risk of both myocardial infarction (as shown here) and cardiovascular death. This increases with the number of cigarettes smoked.⁹⁻¹¹ In this study we also found that after occlusion of a single major coronary artery left ventricular function was more depressed in heavy smokers than in a group of light and non-smokers with similar lesions. This association is independent of the site of arterial occlusion, the size of distribution of the artery, and a history of infarction and suggests that cigarette smoking independently affects the amount of myocardial infarction that results from the occlusion of a particular artery.

Support for this suggestion comes from a study of 3997 patients undergoing coronary angiography which showed a greater frequency of previous myo-

cardial infarction in smokers than in non-smokers with coronary artery disease of comparable severity.¹² Left ventricular function was not assessed in that study, however, and the inclusion of a heterogeneous group of patients with multivessel disease makes separation of the effects of smoking difficult. Epidemiological studies have also shown that although smoking is strongly related to myocardial infarction and death, the relation to angina pectoris is modest, if it exists at all.¹³ These findings also suggest an independent effect of cigarette smoking on the likelihood and size of myocardial infarction.

Acute thrombosis of a previously chronically narrowed coronary vessel is the pathogenic mechanism responsible for most transmural myocardial infarctions¹⁴ and cigarette smoking may promote thrombosis by increasing platelet aggregation and adherence.¹⁵⁻²⁰ Cigarette smoking seems to affect the biochemical composition of atherosclerotic plaques²¹ and this may influence their rates of growth and thrombogenic potential. A recent study has also shown that production of prostacyclin, a potent vasodilator and platelet antiaggregatory agent produced by vascular endothelial cells, is depressed in smokers.²²

The importance of these smoking induced changes lies in their potential for altering the time course over which occlusion of a vessel takes place and consequently the amount of left ventricular damage that results. We suggest that cigarette smoking mainly affects ventricular function by promoting thrombus formation at sites of atherosclerotic narrowing, and that in smokers the development of sudden complete occlusion may be more likely than progressive gradual narrowing of non-critically narrowed vessels. The consequences for left ventricular function will be great because the time taken for a stenosis to develop has a major bearing on the development and size of collateral vessels in both animal and human studies^{23,24} and collateral flow is a major determinant of the amount of myocardial damage occurring after coronary occlusion.²⁰ Our finding that there was no significant difference in collateral score between patients with good and impaired left ventricular function may simply reflect the fact that coronary angiography only visualises epicardial coronary arteries with diameters $>100\ \mu\text{m}$. Most human collaterals are smaller than this and are sub-endocardial. Therefore, the number and size of collaterals identified at angiography may have only limited relevance to collateral flow.²⁵

Changes in heart rate, blood pressure, plasma catecholamines, and carboxyhaemoglobin concentrations are also seen in smokers and these provide further potential mechanisms through which cigarette smoking may influence infarct size. Other

variables such as autonomic tone and drug treatment at the time of infarction may also be important. Whatever the mechanisms, however, the present study identifies a clear cut association between smoking and ventricular function among a group of symptomatic and asymptomatic patients with occlusion of the left anterior descending coronary artery. Furthermore, the power of the association we found strongly suggests that the smoking habit is an important independent determinant of left ventricular function in patients with ischaemic heart disease.

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Morphological characteristics of clinically significant coronary artery stenosis in stable angina

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SUMMARY All segments of clinically significant stenosis in the coronary arteries of 54 men with stable angina were categorised according to the position of the plaques (eccentric or concentric) and the presence or absence of a pool of extracellular lipid. In the group as a whole, stenosis of $>50\%$ by diameter was caused by concentric fibrous plaques in 48% of lesions, by concentric lipid plaques in 28% , by eccentric fibrous plaques in 12% , and by eccentric lipid plaques in 12% . In addition, 43 of the 54 patients had one or more stenoses with multiple channels (recanalisation). Eccentric plaques with an arc of normal vessel wall occupying more than 16% of the circumference of the residual lumen were considered to have a vasospastic potential and made up 15% of all lesions with stenosis of $>50\%$ by diameter. Forty four per cent of plaques causing stenosis between 30% and 50% by diameter were eccentric and retained a considerable arc of normal media. These lesions were often in series with segments of higher grade stenosis that did not have an arc of normal media. The overall frequency of plaque types gave no indication of the proportions of different plaque types within an individual. In 15% of patients all the plaques causing $>50\%$ diameter stenosis were fibrous and in 13% of patients all the plaques were of the lipid type. Most patients had mixtures of all plaque types in varying proportions. Plaques with a large pool of lipid were not found in 33% of patients whereas they formed $>90\%$ of the plaques in 9% of patients. No segments of stenosis $>50\%$ by diameter with a vasospastic potential were found in 44% of the patients but one or more such plaques was present in the remaining 56% . Three patients (6%) each had five separate segments of stenosis with a vasospastic potential.

The results indicate that even in a population of men with stable angina in whom diabetes is excluded the distribution of types of atheromatous lesions is very heterogenous.

In vivo coronary angiograms demonstrate that pharmacological intervention can lead to significant changes in the diameter of the residual lumen in some stenotic coronary arteries.¹ The variation of lumen diameter showed by such coronary angiograms and referred to as "dynamic stenosis" has been reviewed² and is thought to occur in the presence of plaques that are eccentric and thus retain an arc of arterial wall containing medial muscle capable of contraction. While stenotic segments with such a

vasospastic potential have been reported to make up 70% of all high grade stenosis³⁻⁵ in other pathological studies they are reported to be rare.⁶ This form of stenosis has been confirmed to be the cause of some cases of unstable angina⁷ and is a possible explanation for spontaneous episodes of silent myocardial ischaemia unrelated to exercise in patients with stable angina.⁸ Case selection may be responsible for the variation in the reported incidence of stenoses with a vasospastic potential and further data are needed to determine whether such lesions are present in all patients with advanced coronary atheroma or are confined to a minority.

The configuration of stenotic segments of coronary artery is also relevant to angioplasty. Clinical studies suggest that some lesions can be dilated by much lower pressures than others and this may imply that there is more than one type of stenosis.^{4,9}

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For these reasons the present study is concerned with defining the morphological appearances, at necropsy, of segments of high grade stenosis, as seen in transverse sections of arteries perfused at systemic pressure, in patients who had a clinical diagnosis of stable angina in life.

Patients and methods

PATIENTS

The study group consisted of 54 men aged 45–69 (mean 59.9) in whom the clinical diagnosis was stable angina. All died suddenly outside hospital within six hours of the onset of symptoms in their last attack, none had consulted a doctor within the previous two weeks, and all had been able to lead a normal active life. A detailed postmortem examination including coronary angiography showed no other cause of death other than stenosis caused by atheroma of $>75\%$ by cross sectional area (50% diameter) in one or more segments of coronary artery. A small number of cases with stable angina found to have aortic valve stenosis at necropsy were excluded from the study. Women were excluded because there were too few of them; patients with known diabetes were also excluded. Evidence of previous healed myocardial infarction, in the form of macroscopic regional scarring, was present at necropsy in 38 of the 54 cases. All the patients have been receiving medical treatment for the control of exercise induced angina for 1–13 years (mean (SD) 4.8 (3.6) years). The patients had not had ambulatory monitoring to detect silent ischaemic attacks but any patient who had been diagnosed as having unstable angina in the last six months was excluded. Four patients had had selective coronary arteriography in life.

METHODS

Postmortem coronary arteriography was performed in all cases. The technique and subsequent processing and histological examination of the major epicardial coronary arteries have been described.^{10 11}

In brief, the method enables detailed histological examination and quantification of representative sections of 3 mm segments of the entire epicardial coronary artery tree, which has been distended at physiological pressure by the controlled injections of a mixture of gelatin and barium sulphate before fixation. Subsequently the position of each segment within the coronary artery tree was determined from postmortem arteriograms. Segments were coded by the modified Greenlane Hospital system.¹² Sections of each 3 mm segment of coronary artery were stained with an elastica/haematoxylin and eosin stain.

MORPHOLOGICAL DEFINITIONS

Examination of histological cross sections of coronary arteries that have been distended before fixation allows a simple morphological classification of stenotic segments. Any segment of stenosis may be due to eccentric (figs 1 and 2) or concentric (figs 3 and 4) intimal thickening; the former may be associated with a vasospastic potential. Any segment of stenosis may consist predominantly of intimal fibrosis (figs 2 and 3) or contain, in addition, a pool of free extracellular lipid containing cholesterol and its esters (figs 1 and 4). It is the latter type that has been described as "soft", with the lipid pool being separated from the vessel lumen by a cap of fibrous tissue. The fibrous plaque may contain small amounts of intracellular lipid but the special feature of the lipid rich plaque is a space within the intima containing extracellular lipid. Segments of stenosis in which the original lumen is filled by fibrous tissue containing several new vascular channels (fig 5) are regarded as representing restoration of flow by organisation rather than by lysis of the previous occlusive thrombus.

A plaque was defined as eccentric if there was an associated arc of normal artery wall (figs 1 and 2). The intima was regarded as normal when it was less thick than the media. The thickness of the media and intima were measured perpendicularly to the internal elastic lamina. When the arc of normal arterial wall was $\geq 16^\circ$ of the perimeter of the residual lumen (fig 6) a potential for vasospasm was presumed. We chose 16° (60° of an arc of vessel perimeter) to make the data comparable with previous studies.³ Segments of stenosis in which there was no

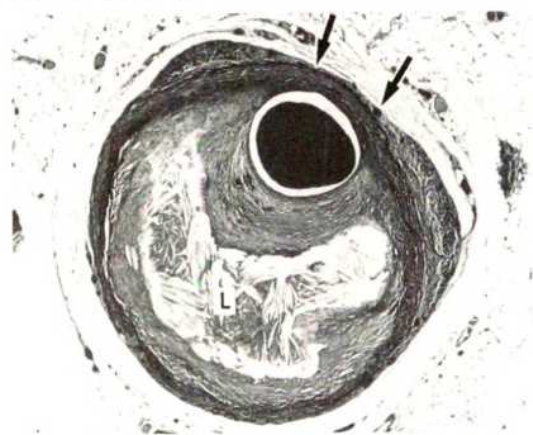


Fig 1 Photomicrograph of transverse section of stenosis caused by an eccentric lipid rich plaque. The lumen contains angiographic medium. An arc of normal vessel wall is indicated (arrows). The thickened intima contains a pool of extracellular lipid (L). Elastica/haematoxylin and eosin stain.

arc of normal arterial wall were defined as concentric (figs 3 and 4). Plaques with a pool of extracellular lipid within the intima were defined as lipid in type (figs 1 and 4). If an extracellular pool of lipid was not present the plaque was defined as fibrous. Segments in which there were several vascular channels within the original lumen (fig 5) were recorded but the degree of stenosis was not measured.

MEASUREMENT

Stained sections of the coronary arteries were measured with a microscope linked to a digitising bit pad and computer. All the sections from each case were measured by two observers. The perimeters of the

internal elastic lamina and residual lumen were measured. All stable plaques (that is those without thrombosis in which the stenosis calculated from the perimeter measurements was $\geq 50\%$ of the cross sectional area corresponding to 30% stenosis or greater by diameter) were coded for the morphological characteristics as defined above. When they were present the circumferential length of arcs of residual normal arterial wall and the area of the lipid pool were also measured.

STATISTICAL METHODS

The proportion of the different morphological types of plaques were compared by the χ^2 test, corrected



Fig 2 Photomicrograph of transverse section of stenosis caused by an eccentric fibrous plaque. There is an arc of normal media adjacent to the lumen. The plaque does not contain a pool of lipid. Elastica/haematoxylin and eosin stain.

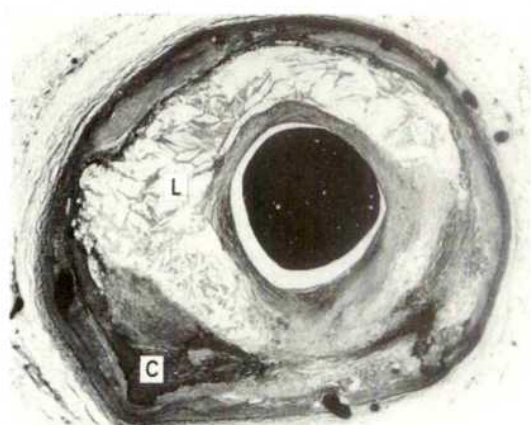


Fig 4 Photomicrograph showing stenosis caused by concentric lipid rich plaque. A pool of lipid (L) almost surrounds the residual lumen. Calcification (C) is also present. Elastica/haematoxylin and eosin stain.

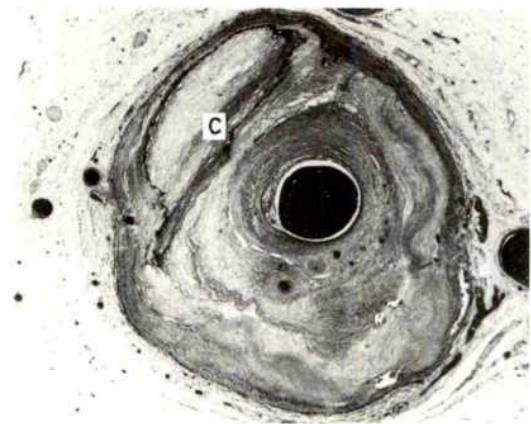


Fig 3 Photomicrograph showing stenosis caused by concentric fibrous thickening of the intima. The small central residual lumen contains angiographic medium. The intima does not contain a lipid pool but there is a plate of calcification (C). Elastica/haematoxylin and eosin stain.

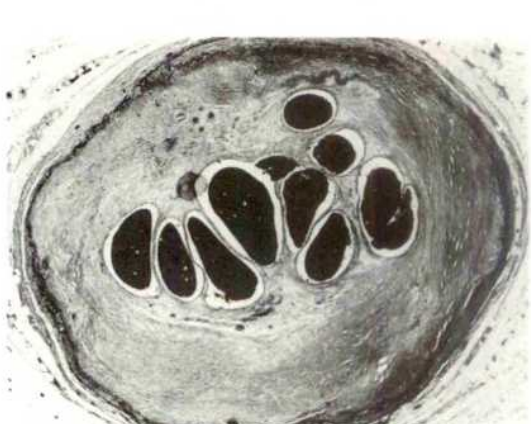


Fig 5 Photomicrograph showing recanalisation of a stenosis. The intima is replaced by connective tissue within which there are nine new vascular channels each containing angiographic medium. Elastica/haematoxylin and eosin stain.

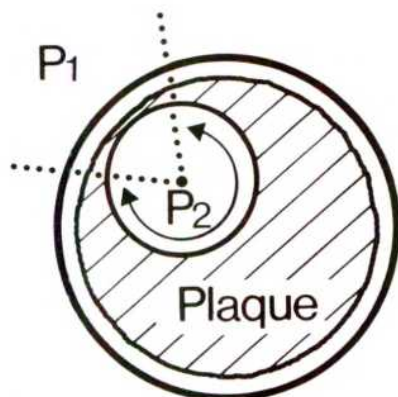


Fig 6 Definition of vasospastic potential. P_1 is the length of the arc of the normal media and is expressed as a proportion of P_1 plus P_2 , that is the perimeter of the residual lumen. The arc subtends an angle of 60° if P_1 is 16% of the circumference of the residual lumen.

for continuity where appropriate. Probability (p) values are given for the appropriate degree of freedom. Means (1 SD) are also given when appropriate. The unpaired t test was used, with correction for unequal sample size and variance, to compare differences in means.

Results

A total of 3480 arterial segments were measured from the 54 hearts.

STENOSES $>75\%$ BY CROSS SECTIONAL AREA (50% BY DIAMETER)

Four hundred and forty eight arterial segments had stenosis of $>75\%$ by cross sectional area. In the 38 cases with healed regional infarction the mean number of stenotic segments (9.5 (6.9) per case) was higher than the mean number in cases without infarction (5.6 (3.3) per case) ($t' = 2.804$, $p < 0.05$).

When all 54 cases were considered 270 (60.3%) of the 448 plaques were fibrous and 178 were lipid (39.7%) with a large lipid pool occupying more than 10% of the intima in most (27.9% of the total). One hundred and six (24%) of the 448 plaques were eccentric and 342 (76%) were concentric. Table 1 shows the overall incidence of the four types of lesion representing combinations of these variables. Those with old infarction had significantly more fibrous plaques than those without (table 2) ($\chi^2 = 20.62$, $p < 0.005$).

There was considerable variability in the distribution of the different morphological types of stenosis between individuals. Eight (15%) of patients had only fibrous plaques while seven (13%) patients had

Table 1 Overall distribution of plaque types in 54 men with stable angina

<i>o_o stenosis by cross sectional area</i>				
<i>≥ 50 to < 75^o_o</i>		<i>> 75^o_o</i>		
CF	282 (41)	} 385 (56)*	216 (48)	} 342 (76)*
CL	103 (15)		126 (28)	
EF	188 (27)	} 308 (44)*	54 (12)	} 106 (24)*
EL	120 (17)		52 (12)	
693 (100)		448 (100)		

* $\chi^2 = 50.02$; $p < 0.005$.

CF, concentric fibrous; CL, concentric lipid; EF, eccentric fibrous; EL, eccentric lipid.

Numbers in parentheses are percentages (rounded).

Table 2 Number of segments showing each morphological pattern by grade of stenoses and presence or absence of old myocardial infarction

% stenosis by cross sectional area				
≥ 50 to $<75\%$		$>75\%$		
A	AI	A	AI	
CF	67 (38)	215 (44)	26 (29)	190 (53)
CL	26 (15)	77 (15)	39 (43)	87 (24)
EF	42 (24)	146 (28)	10 (11)	44 (12)
EL	43 (24)	77 (15)	15 (17)	37 (10)
$\chi^2 = 8.16$, $p < 0.05$		$\chi^2 = 20.62$, $p < 0.005$		

A, Angina alone; AI, angina and old myocardial infarction; CF, concentric fibrous plaque; CL, concentric lipid plaque; EF, eccentric fibrous plaque; EL, eccentric lipid plaque. Numbers in parentheses are percentages (rounded).

virtually all lipid plaques and very few fibrous plaques (fig 7). In five (9%) patients plaques with a large pool of lipid (fig 8) were the only lesions whereas 18 (33%) patients had no lesions of this type. Between these extremes were patients with varying proportions of the two types of plaques with the lipid pool occupying $>10\%$ of the intima in some.

Of the 106 plaques that were eccentric 69 (15% of the total number of plaques causing stenosis of $>75\%$ of the cross sectional luminal area) had a vasospastic potential as defined as a medial segment of $\geq 16\%$ of the perimeter of the residual lumen. There was also considerable variation in the distribution of eccentric plaques (fig 9). Twenty (37%) patients had no plaques of this type while in four (7%) patients all of the plaques were eccentric. Table 3 shows the uneven distribution of eccentric plaques with a retained arc of normal medial muscle sufficient to allow a vasospastic potential.

STENOSES $>50\%$ BUT $<75\%$ BY CROSS SECTIONAL AREA

Cases with angina and old myocardial infarction had more stenotic segments of this degree (13.6 (7.1) per

case) than those with angina alone (11.1 (4.8) per case), although this difference was not significant ($t = 1.504$, $p < 0.05$). Of the total of 693 plaques with this degree of stenosis, 470 (67.8%) were fibrous and 223 were lipid (32.2%). Eccentric

plaques made up 308 (44%) of the 693 plaques. As for the higher grade lesions there was a difference in the distribution of the morphological types of plaque (table 2) ($\chi^2 = 8.16$, $p < 0.05$) between those with and those without old myocardial infarction.

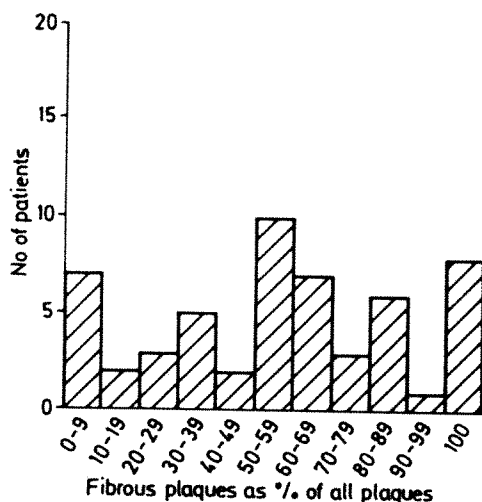


Fig 7 Histogram showing the number of patients in the whole study ($n = 54$) with fibrous plaques that caused $> 75\%$ stenosis by cross sectional area. The results are expressed as a percentage of the total number of plaques per case causing $> 75\%$ stenosis by cross sectional area. Interval ranges are indicated.

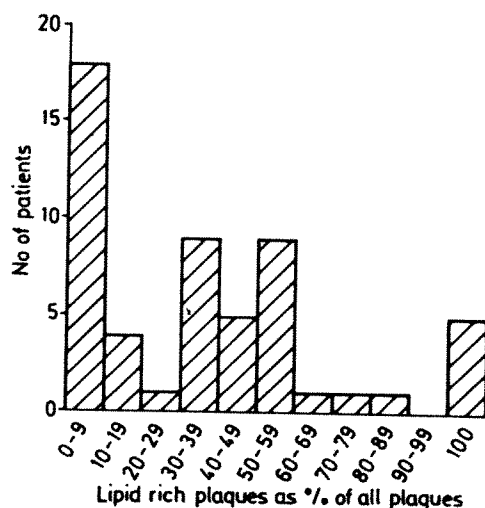


Fig 8 Histogram showing the number of patients in the whole study ($n = 54$) with lipid rich plaques that caused $> 75\%$ stenosis by cross sectional area. The results are expressed as a percentage of the total number of plaques per case causing $> 75\%$ stenosis by cross sectional area. A lipid rich plaque is defined as a lipid pool occupying $> 10\%$ of the intima area. Interval ranges are indicated.

COMPARISON OF HIGH AND LOW GRADE STENOSIS

The proportion of eccentric plaques becomes lower, and conversely the proportion of concentric plaques higher, with increasing stenosis ($\chi^2 = 50.02$, $p < 0.005$). The proportional rise in concentric lipid plaques is greater than that of concentric fibrous plaques. Patients with evidence of old myocardial infarction showed significantly more concentric fibrous plaques, particularly at high grade stenosis, than patients without evidence of old myocardial infarction (table 2).

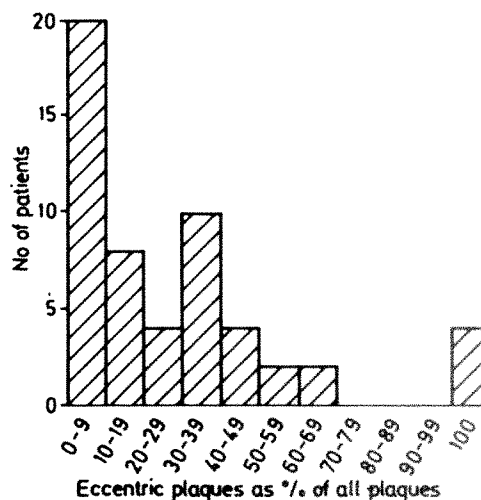


Fig 9 Histogram showing the number of patients in the whole study ($n = 54$) with eccentric plaques (both fibrous and lipid) causing $> 75\%$ stenosis by cross sectional area. Results are expressed as a percentage of the total number of plaques per case causing stenosis $> 75\%$ by cross sectional area. Interval ranges are indicated.

Table 3 Number of cases with segments having a vasospastic potential and $> 75\%$ stenosis by cross sectional area

	Number of segments					
	0	1	2	3	4	5
No of cases ($n = 54$)	24 (44)	12 (22)	7 (13)	4 (7)	4 (7)	3 (6)

Numbers in parentheses are percentages (rounded).

RECANALISED SEGMENTS

In addition to the stenoses already classified, 43 of the 54 cases had one or more arterial segments in which the lumen was multichannelled. Thirty three (86.8%) of the 38 patients with old myocardial infarction had such segments as did 10 (62.5%) of the 16 without old myocardial infarction ($\chi^2 = 2.636$, $p > 0.10$).

Discussion

The present study confirms that in some segments of stenosed coronary artery in patients with stable angina there is the potential for the degree of obstruction to vary with vasomotor tone. When all the segments with stenosis of $>75\%$ by cross sectional areas ($>50\%$ diameter) were considered, plaques in which an arc of normal media remained ($\geq 16\%$ of the perimeter of the residual lumen) were found in 15% of the 448 lesions. This figure is in broad agreement with two other studies that reported a frequency of 15% and 20% .^{6,13} It contrasts, however, with other studies in which 70% of high grade stenotic lesions had a vasospastic potential³⁻⁵ and in which methods and definitions similar to those in the present study were used. The considerable variation in the distribution of plaque types from individual to individual, however, means that any figure based on pooled data gives no indication of the distribution in an individual. In some individuals all the plaques have a vasospastic potential, in others there are no such lesions. Twenty four of the 54 patients with stable angina in the present study had no lesions of this type. Patients with stable angina might be expected to have the lowest frequency of stenoses with vasospastic potential. Any study that includes patients with acute manifestations of ischaemic disease, in particular unstable angina, might have a far higher frequency of potentially vasospastic stenosis.

The potential for vasoconstriction within a stenotic segment depends on two morphological features. The first is the presence or absence of normal media. In arteries which have been distended to physiological pressures during fixation the plaque bulges outward and not inward (fig 10); the lumen is approximately round in cross section although the cross sectional area is considerably smaller than that of adjacent segments of normal artery. Behind the plaque the elastic lamina of the artery wall is often disrupted and the broken ends form coils at the margin of the plaque (fig 11); the media behind the plaque is thinned or even totally lost. In concentric plaques medial muscle may therefore be absent, whereas in eccentric plaques the arterial wall opposite the plaque has a normal elastic lamina and

medial muscle of normal thickness and therefore a potential for vasoconstriction.

The second factor preventing vasoconstriction in concentric lesions is the splinting produced by intimal fibrosis and calcification (figs 3 and 4) that is effective even when medial muscle is retained. It is not known how thick the intima must be for the fibrosis to prevent alterations in lumen area with vasomotor tone; we have adopted the arbitrary definition of an intima that exceeds the media in

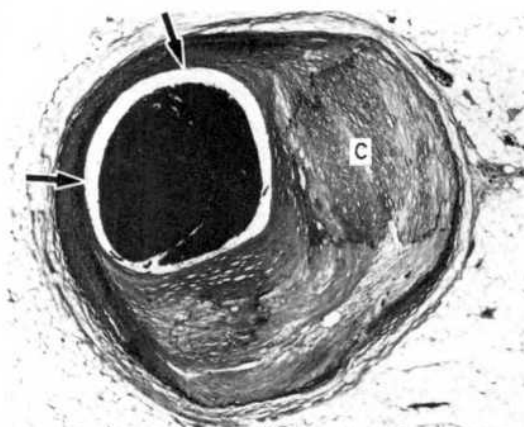


Fig 10 Photomicrograph showing stenosis caused by an eccentric fibrous plaque. The lumen is round because the bulk of the plaque has been extruded outward at the expense of the media. The plaque contains a plate of calcification (C). Opposite the plaque there is a large arc of normal vessel wall (arrows) over which the intima is normal. Elastic/hæmatoxylin and eosin stain.

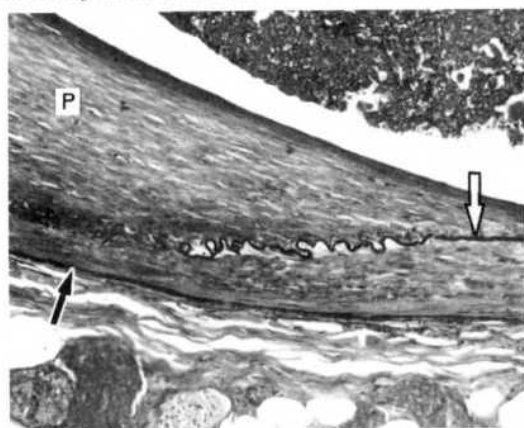


Fig 11 Photomicrograph showing the vessel wall at the margin of an eccentric plaque. Behind the plaque (P) the media is thinned (black arrow). The internal elastic lamina is coiled and broken at the margin of the plaque. Within the arc of normal vessel wall the elastic lamina is straight and the media is of normal thickness (white arrow). Elastic/hæmatoxylin and eosin stain.

thickness. Clinical evidence, based on angiography, suggests that it is only eccentric lesions which vary in diameter with infusion of ergometrine and that the presence of an arc of normal vessel wall is the dominant determinant of the presence or absence of a vasospastic potential.¹

There has been considerable discussion about the exact degree of pre-existing narrowing of the lumen in relation to the size of the arc of normal media around the residual lumen that can lead to vasospastic angina.^{2,3,7} To make our data comparable with previous studies we adopted the arbitrary criterion that a segment of normal media occupying more than a 60° arc of the vessel perimeter would give a potential for vasospasm.³ The theoretical basis for this figure is that in segments with >75% stenosis by cross sectional area a shortening of 10% in the media will appreciably reduce flow. The calculation assumes that a 10% reduction in length is normally found when smooth muscle cells contract. Whereas this assumption may be true in physiological vasoconstriction, spasm¹⁴ could lead to far greater degrees of medial shortening and could create important obstruction at sites where the fixed stenotic element is <75% by cross sectional area.

Where there is stenosis of 50–75% by cross sectional area 44% of lesions occur in arterial segments with a retained arc of medial muscle; most of these will be in series with segments of higher grade stenoses that are not capable of vasospasm.

A further and entirely unquantifiable variable is the physical properties of the plaque and the thickened intima adjacent to the plaque. Eccentric fibrous plaques may be less flexible than eccentric lipid rich plaques in which the intima contains a pool of lipid which, depending on its chemical composition, may or may not be in the liquid phase.¹⁵ Calcification could also splint the wall of the artery and prevent alteration in the cross sectional area of the lumen.

Postmortem studies cannot prove the existence of vasospasm in life; they can only demonstrate the presence or absence of plaques with morphological characteristics that make them capable of vasospasm. Selection of patients by different clinical criteria may specifically select patients with a preponderance of one type of plaque; thus it is feasible that a subgroup of patients with predominantly stable angina will have one or more lesions capable of variation in cross sectional area and responsible for episodes of ischaemia. There is clinical evidence to support this view; some patients with classic stable angina suffer a reduction in cross sectional area of stenotic segments on exercise while the normal vessel dilates.¹⁶ The pathological findings are consistent with the view that there is a clinical spectrum from patients with fixed stenosis who have angina

precipitated only by a predictable level of exercise to patients who have angina precipitated at rest by variations in the cross sectional area of the vessel lumen.¹⁴

Differences in plaque morphology are relevant to the methods by which successful angioplasty may be achieved^{4,5} and by which subsequent restenosis⁴ may occur. Generalisations about the relative frequencies of the types of plaque in a population with stable angina are of limited value because of the heterogeneity of the morphological types of plaques found in individuals. It is not possible to predict what types of plaques are present in an individual. Further, the characteristics of one plaque in an individual will not predict those of another plaque. Most patients with stable angina will have a mixture of all plaque types.

The presence or absence of plaques with a lipid pool may be relevant to individual prognosis. Plaques of this type have the greatest propensity to develop overlying thrombosis¹⁷ and thus acute infarction. Some patients with stable angina are at low risk because they do not have such plaques.

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Effect of the specific thromboxane receptor blocking drug AH23848 in patients with angina pectoris

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SUMMARY The effect of the specific thromboxane receptor blocking drug AH23848 was investigated in two double blind placebo controlled studies in male patients with exercise induced angina pectoris and angiographically verified coronary lesions. In the first study cardiac pacing was performed in twenty patients after coronary angiography. Patients were then randomised into two groups and received either AH23848 (70 mg orally) or placebo. One hour later cardiac pacing was repeated. Neither treatment had any significant effect upon time to angina or the rate-pressure product at the onset of chest pain in these patients. In the second study twenty male patients were randomised to seven days' treatment with AH23848 (70 mg three times a day) or placebo followed by a crossover to the other treatment for a further seven days. Clinical assessment was performed before treatment and at the end of each treatment period. There was no significant difference between the placebo and AH23848 treatment periods in exercise tolerance, the rate-pressure product at angina after exercise testing, the number of ischaemic attacks as determined from 24 hour ambulatory electrocardiograms, the number of attacks of pain, or the number of glyceryl trinitrate tablets consumed. This lack of a clinical effect with AH23848 was seen despite a profound inhibition of ex vivo platelet aggregation stimulated by the thromboxane A_2 -mimetic U-46619. Because in experimental animals in vivo AH23848 blocks vascular thromboxane receptors as well as platelet thromboxane receptors the lack of effect of AH23848 in cardiac pacing and exercise induced angina is unlikely to be the result of inadequate blockade of thromboxane receptors. The lack of effect of the drug is more likely to indicate that thromboxane A_2 is not a factor in the aetiology of the pain experienced by these patients during exercise or cardiac pacing.

Angina pectoris is the clinical manifestation of an imbalance between myocardial oxygen demand and the supply capabilities of the coronary arterial system. Most patients with angina have considerable fixed coronary obstruction by atheroma. But there has been much interest in the possibility that dynamic coronary obstruction produced by changes in tone of the coronary vessels or temporary obstruction by platelet thrombi may also play a part. Thromboxane A_2 is released from activated platelets and is a potent inducer of platelet aggregation^{1 2} and a powerful contractile agent in both animal and

human coronary arteries in vitro.³ This profile of activity led several workers to propose a role for thromboxane A_2 in coronary vasospasm leading to myocardial infarction, sudden cardiac death, and variant angina.^{4 5}

The evidence for a role of thromboxane A_2 in human angina is, however, equivocal. There have been several reports that concentrations of thromboxane B_2 , the stable degradation product of thromboxane A_2 , is raised in coronary sinus blood from patients with unstable angina⁶⁻⁸ or during cardiac pacing in patients with angina.^{9 10} Aspirin at doses that reduced serum or urinary concentrations of thromboxane B_2 by >75% was, however, without effect upon the frequency of ischaemic incidents in patients with variant angina.^{11 12} In contrast two studies have recently shown aspirin to be effective in

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reducing the frequency of myocardial infarction in patients with unstable angina.^{13 14} Equivocal results have also been reported with the thromboxane synthetase inhibitor, dazoxiben, which has been reported either to reduce^{15 16} or to leave unaltered^{17 18} the ischaemic response to atrial pacing or exercise in patients with coronary artery disease.

Evidence derived from drugs that interfere with synthesis of thromboxane A₂ is, however, difficult to interpret. If the inhibition of thromboxane A₂ is achieved by inhibition of fatty acid cyclo-oxygenase the formation of other biologically active prostanooids such as prostacyclin, prostaglandins D₂ and E₂ will also be inhibited, and if it is achieved by inhibition of thromboxane synthetase the production of the other products of the cyclo-oxygenase pathway may be enhanced.¹⁹ Thus in neither case it is possible to relate the end result solely to a deficiency of thromboxane A₂. The ideal compound to determine the role of thromboxane A₂ in disease states is therefore one that specifically blocks the actions of thromboxane A₂ at the level of the receptor.

AH23848 is such a drug. It has no action on cyclo-oxygenase, thromboxane synthetase, prostacyclin synthetase, or cyclic adenosine monophosphate phosphodiesterase enzymes.²⁰ Over the same concentration range in vitro it inhibits platelet aggregation induced by thromboxane A₂ and its stable mimetic U-46619²¹ and contraction of vascular smooth muscle from various species.^{22 23} Most importantly, AH23848 is also equipotent in blocking platelet and vascular smooth muscle thromboxane receptors in animals in vivo²² and would thus be expected to block both the vascular and platelet effects of thromboxane A₂ in disease states. The compound is orally active and long acting in human volunteers^{24 25} and is active in certain animal models of occlusive vascular disease and ischaemia.^{20 26 27}

We have therefore studied the effects of orally administered AH23848 in patients with exercise induced angina pectoris and angiographically verified coronary lesions in an attempt to clarify the role of thromboxane A₂ in this disease state. We chose to study this group rather than patients with unstable or "vasospastic" angina because the latter are much more difficult to define as a homogeneous group and their symptoms are often capricious and hard to reproduce. The study was conducted in two parts: as a placebo controlled double blind trial of the effect of a single dose of AH23848 on pacing induced angina and as a double blind crossover trial of 70 mg AH23848 three times daily for one week against placebo with assessment by exercise testing, ambulatory electrocardiogram monitoring, patient

diaries, and glyceryl trinitrate tablet counts. In both groups of patients the magnitude of thromboxane receptor blockade produced by AH23848 was determined on platelets *ex vivo* so that any clinical effect of the drug could be correlated with its pharmacological effect.

Patients and methods

The studies were approved by the local advisory ethics committee. Consecutive male patients admitted for diagnostic coronary arteriography because of angina pectoris not adequately controlled by medical treatment were invited to enter the trials. Patients were excluded if they had left main coronary stenosis or had experienced a recent myocardial infarction. Their written informed consent was obtained.

PACING INDUCED ANGINA

Patients were studied at the time of coronary arteriography, which was performed by the Judkins technique²⁸ without heparinisation. Previous medication was discontinued at the time of hospital admission 24 hours before the study. After angiography a bipolar pacing catheter was inserted percutaneously via an arm or leg vein and positioned in the right atrial appendage. Before pacing, blood pressure was measured by sphygmomanometer cuff and auscultation. In the first study blood pressures were checked against intra-arterial blood pressures. Pacing was then started at 100 beats per minute and the rate was increased by 10 beats per minute every 20 seconds until either a rate of 140 beats per minute was reached or the maximum rate at which 1:1 atrio-ventricular conduction could be maintained was achieved. Pacing was continued until the patient experienced chest pain or for five minutes, whichever was the shorter. The duration of pacing, maximum pacing rate achieved, and the blood pressure at the onset of angina were recorded. The product of pacing rate and systolic blood pressure was then determined (rate-pressure product). The patient was then given 70 mg AH23848 or a placebo capsule with 100 ml water. One hour later blood pressure was measured and pacing was then repeated and the same variables were recorded as before. The pacing electrode was then removed. The placebo group was introduced to control for the possibility that the patient might "learn" the time to angina, or alternatively be more relaxed and have a higher angina threshold at the time of the second pacing study. The long duration of action of AH23848²⁴ precluded any acute crossover study.

EXERCISE INDUCED ANGINA

Patients admitted to this part of the trial all had a positive Bruce protocol exercise test²⁹ and had undergone diagnostic coronary arteriography. They included four patients who had taken part in the first study; but at least one month had elapsed between the two studies. Before starting the study patients were clinically examined and had a 12 lead electrocardiogram, a Bruce protocol exercise test, and a 24 hour ambulatory electrocardiogram recording with two-channel frequency modulated Tracker equipment.³⁰ Blood pressure was measured with a sphygmomanometer before and at one minute intervals during exercise testing. The electrocardiogram was monitored throughout exercise and the rate-pressure product at the time of onset of angina was calculated. Patients were issued with counted glyceryl trinitrate tablets and with diaries in which to record angina attacks and record the number of glyceryl trinitrate tablets taken. Previous antianginal treatment with β adrenoceptor antagonists, calcium channel blockers, or sustained release nitrates was not stopped nor was it altered during the trial. Patients were asked not to take aspirin or other non-steroidal anti-inflammatory agents during and for two weeks before the trial. Patients were allocated in random order to AH23848 70 mg three times daily one hour before meals or to identical placebo capsules. After six days of the seven day treatment period clinical examination and exercise testing were repeated. On the day of exercise testing the time of the morning treatment was adjusted so that the exercise test took place two hours after dosing. An ambulatory electrocardiogram was recorded for 24 hours on the seventh day of the treatment period. Diaries and unused glyceryl trinitrate tablets were collected and a fresh diary and supply of glyceryl trinitrate were issued. The patient then crossed over to the alternative treatment for a further week and the tests were repeated as before. As well as comments recorded in the diaries, subjective side effects were recorded on a standard questionnaire. Blood samples for routine laboratory investigations (urea, electrolytes, liver function tests, and full blood count) were taken before treatment and after each week's treatment.

STATISTICAL ANALYSIS

Results were analysed by appropriate non-parametric statistics. For the second study we used Koch's method of applying these to a two period crossover trial.³¹ In addition we used methods based on Wilcoxon's rank sum statistic to compare AH23848 and placebo groups and to derive confidence intervals for each data set.³² Data for each of the measured variables were analysed separately.

PLATELET AGGREGATION

Blood was obtained from patients by venepuncture from an antecubital vein and anticoagulated with trisodium citrate. Platelet aggregation in response to the stable thromboxane A_2 mimetic U-46619 and adenosine diphosphate was monitored by a previously reported technique.³³ Briefly, the number of single platelets in a 0.5 ml volume of whole blood were counted electronically before and at intervals after addition of an aggregating agent. The peak fall in platelet count was recorded and expressed as a percentage of the control count for that volume. By adding a different concentration of aggregating agent to separate volumes of blood, aggregation concentration-effect curves were constructed (see legend to fig 1 for further experimental details).

Concentration ratios were calculated where possible on the parallel parts of the aggregation concentration-effect curves. The concentration of aggregating agent required to give 50% aggregation (EC_{50}) after treatment was divided by the mean EC_{50} taken from the duplicate pre-treatment control curves (see below).

Pacing-induced angina

Duplicate blood samples for control platelet aggregation studies were taken fifteen minutes apart and before angiography. A third blood sample was taken immediately after the first pacing period and a further sample one hour after treatment but before pacing. Finally, a further sample was taken immediately after the second pacing period.

Exercise-induced angina

During the pre-treatment examination of patients, but before exercise testing, duplicate blood samples for ex vivo platelet aggregation studies were taken approximately 30 minutes apart. A further sample was taken immediately after the exercise test. On the subsequent two visits single blood samples were taken before and immediately after the exercise test.

DRUGS USED

Glaxo Group Research Ltd supplied white opaque unmarked hard gelatin capsules each containing the equivalent of 35 mg AH23848 acid as the calcium salt or placebo. Trisodium citrate (BDH) was prepared as a 0.129 mol/l solution in distilled water. Acetylsalicylic acid (aspirin, BDH) was dissolved in TRIS hydrochloride (HCl) buffer (100 mmol/l, pH 8.5) to give a stock solution of 10 mg/ml. Adenosine diphosphate (Sigma) was dissolved in Tris HCl buffer (100 mmol/l, pH 6.5) to give a solution strength of 1.0×10^{-2} mol/l, dilutions were prepared in 0.9% wt/vol sodium chloride solution (saline). U-46619 (Glaxo Group Research) was pre-

Table 1 Effect of AH23848 (70 mg) or placebo upon the time to angina and the rate-pressure product in patients with coronary artery disease undergoing cardiac pacing

Case No	Pre-treatment		Post-treatment		Ratio of post: pretreatment RPP
	Time to angina (min)	RPP	Time to angina (min)	RPP	
AH23848.					
01	5.0	19800	3.5	20400	1.03
03	5.0	13800	5.0	14950	1.08
06	5.0	12350	5.0	12610	1.02
07	1.5	14300	1.5	15950	1.12
10	5.0	12100	5.0	13200	1.09
12	3.0	15600	5.0	21450	1.38
13	5.0	14400	5.0	13200	0.92
14	5.0	14300	5.0	18200	1.27
19	3.5	14375	5.0	13750	0.96
20	1.5	15600	2.5	13200	0.85
Placebo.					
02	5.0	13800	5.0	8970	0.65
04	5.0	14300	5.0	11050	0.77
05	5.0	11760	5.0	11400	0.97
08	5.5*	9900	5.0	11500	1.17
09	5.0	10925	5.0	11270	1.03
11	5.0	18900	5.0	16200	0.86
15	5.0	14175	5.0	15120	1.07
16	3.5	11700	3.0	14300	1.22
17	3.0	14300	4.5	17550	1.23
18	1.5	20000	4.5	13750	0.69

RPP, rate-pressure product.

*Pacing continued for 5.5 minutes in this patient.

pared as a 1.0×10^{-2} mol/l solution in 1% wt/vol sodium bicarbonate in saline; dilutions were prepared in saline. All drug solutions were stored on ice during use. All concentrations of drugs refer to whole blood.

Results

PACING-INDUCED ANGINA

Twenty male patients with stable angina were entered into this study. Of these patients 13 had three vessel disease, four had two vessel disease, and three had single vessel disease. Fourteen patients subsequently went on to have coronary artery bypass graft surgery. The age distributions were similar for the two groups of patients, the median and range being 54 (40–59) years for placebo and 56 (41–65) years for AH23848. There was no significant difference between the groups in pre-catheter exercise tolerance, coronary artery score, or subsequent requirement for coronary surgery.

In both groups of patients treatment had no effect on the time to angina, the mean (range) in minutes before and after placebo being 4.4 (1.5–5.5) and 4.7 (3.0–5.0) respectively compared with 4.0 (1.5–5.0) and 4.3 (1.5–5.0) before and after AH23848. The rate-pressure product was similarly unaffected by either treatment (table 1). Diastolic blood pressure at the onset of angina was significantly higher in

patients receiving AH23848 than in patients receiving placebo (median difference (95% confidence interval) 13 (5, 30) mm Hg). In contrast, diastolic pressure was not higher in the AH23848 group before pacing nor was such a difference seen at angina during the pre-treatment pacing. In addition, no such difference in systolic blood pressure was seen between the two groups of patients either before pacing or at angina. The reason for the slightly higher diastolic blood pressure at angina after AH23848 treatment is not known.

Despite the apparent lack of effect of AH23848 upon the variables assessed during pacing, this agent did have a profound effect upon U-46619-induced ex vivo platelet aggregation in blood samples taken one hour after drug treatment. In all of the patients given AH23848 a profound rightward displacement of the U-46619 concentration effect curve was seen. In only one patient was a U-46619 concentration ratio of <50 obtained (range 19–251); in contrast platelet aggregation induced by adenosine diphosphate was not affected by AH23848 treatment. Placebo treatment was also without effect upon aggregation in response to both aggregating agents. Figure 1 shows the mean aggregation concentration-effect curves for the two groups.

During this study blood samples were taken immediately after the end of cardiac pacing. These were taken to determine whether pacing per se pro-

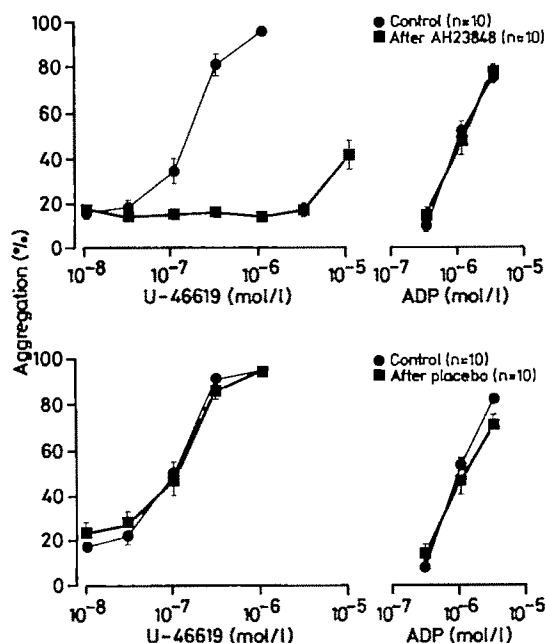


Fig 1 The effect (mean (SE)) of a single oral dose of either AH23848 (70 mg) (upper panel) or placebo (lower panel) upon platelet aggregation induced by U-46619 and adenosine diphosphate (ADP) *ex vivo* in whole blood from patients with angina pectoris undergoing cardiac pacing. Blood samples (4.5 ml) were obtained by venepuncture and anticoagulated with trisodium citrate (final concentration 12.9 mmol/l). Volumes of whole blood were then incubated at 37°C in a shaking water bath while aggregation studies were performed. Aspirin (2.0 mmol/l) was added to blood volumes to prevent the formation of endogenous prostaglandins during the aggregation process. Aggregation studies were started as rapidly as possible, usually 10–15 minutes after venepuncture. Platelet counts were determined before and 10, 20, and occasionally 30 minutes after addition of U-46619, the peak fall in platelet count usually occurring at 10 minutes in control and placebo blood samples but up to 30 minutes after AH23848 treatment. Platelet counts were determined before and one minute after addition of adenosine diphosphate (ADP); this has previously been shown to represent the time of peak aggregation.^{3,4} The control curves represent the second of the two preliminary U-46619 and adenosine diphosphate curves.

duced any change in platelet sensitivity and whether treatment with a thromboxane receptor blocking drug would modify any such change. Comparison of the EC₅₀ values of the control concentration effect curves in response to both U-46619 and adenosine diphosphate with those from curves obtained after the first pacing period from the twenty patients showed no consistent change in platelet sensitivity

that could be attributed to pacing.

Few side effects were noted in this study. One patient became dizzy and hypotensive after taking placebo, one experienced nausea 30 minutes after taking AH23848, and a third patient experienced chest pain not typical of angina one hour after taking AH23848 but before the second pacing.

EXERCISE-INDUCED ANGINA

Twenty male patients including four who had taken part in the pacing-induced angina study, entered the study. Of these patients 13 had three vessel disease, four had two vessel disease, and two had single vessel disease (the remaining patient was withdrawn, see below). Eleven patients subsequently went on to have coronary artery bypass graft surgery. Two patients did not complete the study: patient 3 was called in for coronary artery surgery after completing only one week of the study and patient 10 was withdrawn before receiving active treatment because of a sudden deterioration in exercise tolerance. Patient 1 inadvertently took only half the dose of AH23848 and was therefore excluded from the analysis. Of the remaining 17 patients platelet aggregation studies indicated non-compliance in three patients (numbers 11, 13, and 17, see below) and in patient 8 aggregation studies were incomplete. Results were therefore analysed twice, both including these patients ($n = 17$) and excluding them ($n = 13$). Both analyses gave the same result.

Table 2 summarises the results. There was no significant difference in exercise tolerance, number of ischaemic attacks (defined as a depression of the J junction by at least 1 mV followed by an ST segment depression sloping downwards detected by ambulatory electrocardiogram monitoring), number of attacks of pain, or number of glyceryl trinitrate tablets consumed between the placebo and AH23848 treatment periods. In addition we found no significant difference between the two treatments in the rate-pressure product at angina after exercise testing nor any effect on blood pressure.

As in the first study, patients receiving AH23848 for six days generally showed a large rightward displacement in the U-46619 aggregation concentration-effect curve. We saw no effect upon adenosine diphosphate induced aggregation. Figure 2 summarises the data for all patients. Patients who received AH23848 as the first treatment showed no residual blocking effect of the drug on day 6 of the subsequent placebo treatment. Patients 11, 13, and 17 unexpectedly displayed low U-46619 concentration ratios after AH23848 (1.7, 0.7, and 5.2 respectively) and were deemed to be non-compliant. This apparent lack of effect after AH23848 treatment was also seen in the blood samples from these

Table 2 Effect of AH23848 or placebo for seven days upon various indices of ischaemia in patients with angina pectoris undergoing exercise stress testing

Case No	Duration of exercise test (min)		No of ischaemic attacks		No of attacks of pain		No of GTN tablets	
	Placebo	AH23848	Placebo	AH23848	Placebo	AH23848	Placebo	AH23848
<i>Placebo followed by AH23848</i>								
02	4.75	4.5	0	4	—	—	24	18
04	1.75	2.75	6	4	53	35	30	20
05	7.5	7.5	0	0	6	3	1	3
06	6.25	5.0	0	0	9	3	9	3
08†	—	—	2	3	5	7	9	13
11†	5.5	6.5	0	0	1	1	2	3
12	5.0	6.0	1	0	3	2	3	2
13†	5.75	6.0	2	7	19	28	82	90
15	10.0	11.0	0	0	2	0	0	0
18	1.7	2.25	0	1	2	2	0	1
<i>AH23848 followed by placebo</i>								
01*	5.0	5.5	0	0	—	—	4	11
03†	—	4.5	—	1	—	—	—	—
07	3.5	3.5	0	0	44	22	90	44
09	3.0	3.0	5	0	22	12	27	25
10*	—	—	—	—	—	—	—	—
14	4.5	4.0	1	0	5	8	8	10
16	3.0	2.7	0	5	18	26	17	19
17†	8.0	7.0	3	4	—	—	—	—
19	2.0	2.0	—	—	28	24	28	25
20	7.5	6.5	—	—	1	6	0	6

*Patients excluded from analysis (see text).

†Analyses performed with and without these patients (see text).

—Measurement not carried out.

patients after the exercise testing, thus ruling out an erroneous platelet aggregation determination. A ratio of 10 was chosen as the limit below which patient non-compliance was assumed. This value was based upon those obtained from patients given AH23848 in the first study and our experience in healthy volunteers taking this dosage regimen.^{24 25}

Placebo did not have a pronounced effect on aggregation in response to U-46619 or adenosine diphosphate, except in patient 17 in whom platelet aggregation in response to the thromboxane A₂ mimetic appeared to be antagonised more by placebo treatment than by AH23848. This was one of the patients deemed to be non-compliant.

The effect of exercise per se upon platelet aggregation was also studied. In blood samples taken immediately after the pre-treatment exercise test there was no consistent change in platelet sensitivity to either U-46619 or adenosine diphosphate.

In the second study two patients experienced malaise and one patient described diffuse muscle aches while taking placebo; one patient had heartburn, nausea, and vomiting while taking AH23848 and one patient reported feeling very tired while taking the active drug. No clinically significant changes in laboratory values were noted.

Discussion

The present study was designed to test the hypothesis that thromboxane A₂ has a role in angina induced by cardiac pacing and exercise in patients with angiographically confirmed coronary artery disease and therefore whether a thromboxane A₂ receptor blocking drug would be therapeutically useful in this condition.

Evidence for an involvement of thromboxane A₂ in various forms of angina has been largely circumstantial. Thus for example raised concentrations of thromboxane B₂ have been measured in coronary sinus blood during pacing in angina patients.^{9 10 17} However, sampling procedures themselves, especially withdrawal of blood through long indwelling catheters, may induce platelet activation and thromboxane A₂ release.³⁴ If platelets are more reactive after cardiac pacing than before pacing, different degrees of activation and hence thromboxane A₂ release may occur with sampling. These raised concentrations would not then necessarily imply a pathophysiological role for thromboxane A₂ per se.

Evidence from drug studies is also difficult to interpret. Negative studies with cyclo-oxygenase

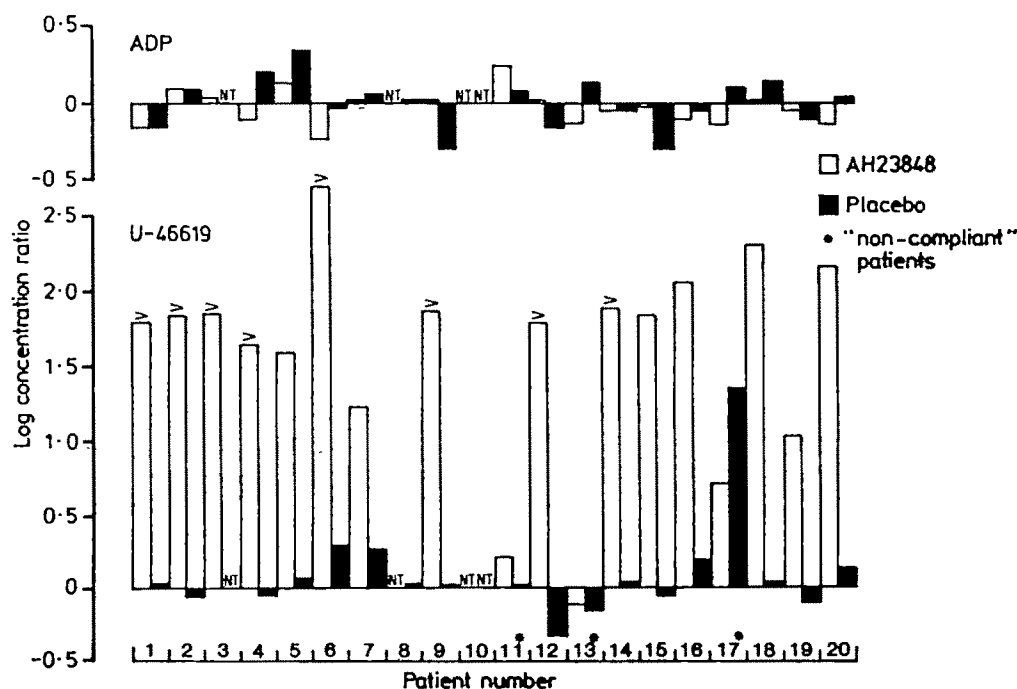


Fig 2 Effect of AH23848 and placebo upon platelet aggregation *ex vivo* in angina patients undergoing exercise tolerance testing. Histograms represent concentration ratios for U-46619 and adenosine diphosphate after treatment with either AH23848 or placebo. Columns designated > represent minimum estimates of U-46619 concentration ratio values when 50% aggregation to U-46619 was not achieved in the post-AH23848 blood samples. In these instances the U-46619 EC_{50} value during treatment was assigned a value of $>1.0 \times 10^{-5}$ mol/l, the highest concentration of aggregating agent used. In patients 11 and 13 there was no antagonism of U-46619-induced aggregation after AH23848 treatment and in patient 17 placebo treatment appeared to be more effective than drug treatment. This profile was not expected from previous experience with the drug. NT, not tested.

inhibitors such as aspirin in pacing-induced angina¹⁶ may be a consequence of the reduction in prostacyclin and platelet-derived prostaglandin D_2 concentrations rather than reduction in thromboxane A_2 itself. The balance between prostacyclin and thromboxane A_2 has been shown to be important in animal models of cardiac ischaemia.³⁵ In contrast, positive findings with the thromboxane synthetase inhibitor dazoxiben^{15,16} could equally well reflect the beneficial diversion of endogenous prostaglandin endoperoxides to prostacyclin rather than to a reduction in thromboxane A_2 concentrations.

As has been pointed out previously²⁰ definitive evidence for the action of thromboxane A_2 in a disease state depends upon the use of a highly specific thromboxane A_2 receptor blocking drug. Such a drug would only block the actions of thromboxane A_2 and leave untouched the production of thromboxane A_2 and prostacyclin. AH23848 is a specific and potent thromboxane A_2 receptor blocking drug

that has no effect upon cyclo-oxygenase, thromboxane synthetase, or prostacyclin synthetase.²⁰ In addition it is non-selective, being approximately equipotent in blocking thromboxane A_2 receptors present on both the platelet and vascular smooth muscle. This profile has been observed both in isolated tissues and *in vivo* in laboratory animals.²² AH23848 would therefore be expected to block local vasoconstriction as well as platelet aggregation induced by thromboxane A_2 *in vivo*.

In the present study AH23848 did not have any clinically beneficial effect on angina pectoris after pacing or exercise in patients with angiographically confirmed coronary artery disease. Platelet aggregation in response to the thromboxane A_2 mimetic U-46619, however, was substantially inhibited by AH23848 at the time of pacing or exercise. Sufficient thromboxane receptor blockade was achieved to produce an approximately 100-fold rightward displacement of the U-46619 platelet aggregation concentration-effect curves. In contrast with the

effect upon U-46619, adenosine diphosphate induced aggregation, which occurs independently of thromboxane A₂ under the conditions of this study, was unaffected. This profile of action would be expected of a specifically acting receptor blocking drug such as AH23848. Thus in the patients studied a very large level of platelet thromboxane A₂ receptor blockade was apparent yet no effect on time to pain was seen in either study. As mentioned above, in experimental studies AH23848 also produces a similar degree of blockade of vascular thromboxane receptors to that produced on the platelet thromboxane receptor. While the pharmacodynamic profile of the actions of this drug upon vascular thromboxane receptor in man has not been studied, both pacing and exercise testing were performed within 1–2 hours of AH23848 administration. Thus it is presumed that a large degree of blockade of the vascular thromboxane receptor was also achieved in these patients. These results are therefore strong evidence for the lack of effect of thromboxane A₂ in angina, at least in the patients we studied and under the circumstances of this study.

In the exercise study several patients were excluded from analysis because there was no antagonism of the U-46619 induced aggregation responses after AH23848. We believed this action to be justified because our experience with the drug in volunteers and patients^{24,25,36} had never shown such a lack of effect. Two analyses performed after inclusion or exclusion of the "non-compliant" patients were both negative.

We believe that the measurement of antagonism of the aggregatory action of U-46619 by AH23848 was essential in the present study so that we could reach valid conclusions about the actions of thromboxane A₂ in these patients. Does this level of thromboxane receptor blockade have any clinical relevance, however? Other studies suggest that it does. Thus in patients with mature aorto-bifemoral arterial Dacron grafts AH23848 appeared to reduce deposition of platelets onto the grafts.³⁶ In the deposition study AH23848 was administered to patients for a similar period (nine days) to that used in the present exercise study and produced a similar level of antagonism of U-46619 induced platelet aggregation. Thus the lack of effect of AH23848 in the present study is unlikely to be caused by an inadequate level of thromboxane receptor blockade.

It could, however, also be argued that since several patients in our study were taking β adrenoceptor antagonists, calcium channel blockers, or nitrates any minor antianginal effect of AH23848 might be overshadowed. Our ethical advisory committee was unhappy about stopping all medication in patients with known severe angina for the trial of

an agent of unproven efficacy. It might be expected that an antianginal agent with a completely different mode of action may have an additive or synergistic effect, however, as has been demonstrated for β adrenoceptor antagonists and calcium channel blockers. The present study does not necessarily contradict observations of increased thromboxane A₂ production in angina, but suggests this is a secondary rather than a primary phenomenon. Nor does it exclude a long term role for platelet activation in extending or perpetuating coronary arterial damage.

Finally, we chose to study patients with exercise induced rather than unstable or vasospastic angina, for the reasons stated in the Introduction and also because we wished to become more familiar with the clinical properties of AH23848 before using it in patients in an unstable state. A priori, vasospastic angina might be more likely to respond to a thromboxane receptor blocking drug. In fact the recent studies with aspirin^{13,14} have provided evidence for the involvement of thromboxane A₂ in this condition. Specific thromboxane receptor blocking drugs like AH23848, by sparing vascular prostacyclin and platelet derived prostaglandin D₂, may prove to be more effective than aspirin.

In conclusion, AH23848 was well tolerated but was without effect upon the indices of ischaemia in patients with pacing and exercise induced angina pectoris despite producing a considerable blockade of the platelet thromboxane A₂ receptor. The results of the present study strongly suggest, therefore, that thromboxane A₂ is not important in severe angina pectoris. AH23848 is a valuable drug, and drugs like it, in addition to resolving the controversy about the involvement of thromboxane A₂ in various diseases, may also prove to be valuable therapeutic agents.

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The haemodynamic response to myocardial ischaemia in ambulant patients with variant angina

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SUMMARY The haemodynamic response to myocardial ischaemia in patients with variant angina during ambulatory activity is unknown. Ambulatory pulmonary artery pressure monitoring with a transducer tipped catheter and simultaneous frequency modulated electrocardiograms was used to assess changes in left ventricular function in five male patients (mean age 51.8 years) during variant angina; four patients had coronary artery stenosis and one had normal coronary arteries. Two hundred and seventy hours of ambulatory recordings were analysed. Twenty episodes (12 painful, 8 silent) of ST segment change > 1 mm occurred. Episodes tended to occur more frequently in the early morning hours. Six episodes of painful ST elevation were associated with a rise in pulmonary artery diastolic pressure. In the remaining episodes ST segment elevation was of shorter duration and there was no rise in pulmonary artery diastolic pressure. Pain was usually a late feature. Silent ST segment elevation occurred at rest and pulmonary artery diastolic pressure increased in all but one episode. Silent exertional ST segment depression was associated with a greater increase in pulmonary artery diastolic pressure than that seen during ST segment elevation. ST segment depression preceded or followed ST segment elevation in two episodes. The onset of ST segment elevation nearly always preceded the onset of a rise in pulmonary artery diastolic pressure. Ergometrine maleate provocation produced a rise in pulmonary artery diastolic pressure in three patients. In one there was no response to $1000 \mu\text{g}$ but spontaneous episodes of ST segment elevation were recorded during ambulatory monitoring. Treadmill exercise resulted in both ST segment elevation and depression with a similar haemodynamic response during both types of electrocardiographic change. When there is important coronary artery disease in two or more vessels ST segment changes may occur in different territories during treadmill exercise and during spontaneous episodes.

Ambulatory pulmonary artery diastolic pressure monitoring is a useful technique for the investigation of variant angina.

In 1959 Prinzmetal *et al* reported on a group of patients in whom angina occurred at rest and was associated with transient cyclic ST segment elevation. Termed variant angina, this syndrome was thought to be secondary to "temporary occlusion of a large diseased artery with a narrow lumen due to an increase in tonus of the vessel wall".¹ Later studies have shown that variant angina is part of a spectrum of "vasospastic myocardial ischaemia" and that variant angina may occur in normal coronary arteries or more commonly in those

with atherosclerotic coronary artery disease.² Myocardial ischaemia during variant angina is thought to result from a reduction in myocardial oxygen supply.^{3,4} ST segment depression during myocardial ischaemia in patients with coronary artery disease is associated with a rise in left ventricular end diastolic pressure.⁵⁻⁷

Previous studies of the changes in left ventricular end diastolic pressure during variant angina have been confined to patients in the coronary care unit or catheter laboratory.² In the present study we assessed the haemodynamic response during variant angina by means of ambulatory pulmonary artery pressure monitoring.

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Table 1 Clinical and angiographic details of patients with variant angina

Patient	Age	Sex	Previous myocardial infarction	Coronary and left ventricular angiography
1	40	M	Inferior	Good LV function, slightly irregular LAD
2	51	M	—	Good LV function, 60% stenosis of proximal first diagonal
3	55	M	—	Good LV function, 90% stenosis of proximal LAD, 90% stenosis of third diagonal
4	62	M	—	Good LV function, irregularities of LAD and Cx, 50% stenosis of proximal RCA
5	51	M	—	Good LV function, normal coronary arteriography

LAD, left anterior descending coronary artery; Cx, circumflex coronary artery; RCA, right coronary artery; LV, left ventricle

Patients and methods

Five male patients (mean age 51.8, range 40–62 years) were studied. Table 1 summarises the clinical, electrocardiographic, and angiographic data. All patients had a relatively short history of anginal chest pain and four patients had rest pain which was mostly nocturnal. Variant angina was defined as ST segment elevation accompanied by chest pain on ambulatory monitoring or ergometrine maleate provocation. Patients 1, 2, 4, and 5 had confirmed coronary artery spasm at the time of ergometrine maleate provocation during coronary angiography.

All antianginal medication other than glyceryl trinitrate was discontinued 48 hours before the study. The protocol was approved by the National Heart Hospital ethics committee and patients gave their informed and written consent.

PULMONARY ARTERY PRESSURE MONITORING

A polyurethane 6 French NIH type catheter with a miniature strain gauge transducer mounted on the tip was used. This was calibrated after immersion in saline for one hour before use. The transducer was driven and demodulated by an electrically isolated Gaeltex pre-amplifier. The catheter was introduced percutaneously via a subclavian vein to a proximal pulmonary artery under fluoroscopy in the cardiac catheter laboratory. The pulmonary artery pressure was recorded on an Oxford Medilog I miniature tape recorder that had been modified by the insertion of an AM4 pressure module.

ST SEGMENT MONITORING

ST segment was monitored on a frequency modulated recorder and leads CM2 and CM5 were recorded. The electrocardiogram was replayed on an Oxford MA20 scanner. Changes in the ST segment were measured 80 ms after the J point to an accuracy of 0.1 mm by means of a magnifying lens equipped with a graticule. A change of 1 mm in the ST segment that lasted >30 seconds was considered to be important. ST segment changes were analysed on a beat to beat basis for five minutes before each episode and again up to five minutes after the ST seg-

ment had returned to basal levels. The pulmonary artery recorder was linked to the frequency modulated electrocardiogram by an event button that marked both the frequency modulated electrocardiogram and the pulmonary artery trace.⁸

CORONARY ARTERIOGRAPHY

Coronary arteriography was performed in all patients by the Judkins' technique from the femoral artery with multiple angiographic projections.

ERGOMETRINE MALEATE PROVOCATION TEST

Patient 1 had had a previously positive provocation test and this test was not repeated. Patients 2–5 underwent ergometrine maleate provocation in the catheter laboratory. A 12 lead surface electrocardiogram was recorded continuously (Siemens Mingograph). Incremental doses of ergometrine maleate were given intravenously every five minutes. The initial dose was 25 µg and this was increased to 50 µg and 100 µg and subsequently by 100 µg and 200 µg up to a maximum to 1000 µg. The test was terminated if there was chest pain, ST segment changes >2 mm, severe hypertension, headache, nausea, or vomiting. Angiographic assessment for the presence of coronary artery spasm was made at the end of the test and was followed immediately by 1–3 mg of intracoronary isosorbide dinitrate. Changes in blood pressure and pulmonary artery pressure were recorded continuously during provocation. Spasm at arteriography was defined as a transient total or subtotal coronary occlusion with delayed distal filling that was reversed by intracoronary nitrates.

AMBULATORY MONITORING

The patients returned to the ward with a pulmonary artery catheter in situ. Continuous monitoring of pulmonary artery pressure was performed with simultaneous recording of frequency modulated electrocardiograms from leads CM2 and CM5. Patients were instructed to keep diaries during the period of ambulatory monitoring and were asked to note the time of onset and severity of chest discomfort as well as their activity at the time of pain. In

Table 2 Response to ergometrine maleate provocation

Patient	Response to ergometrine (+/-)	Dose of ergometrine (μ g)	Magnitude of ST segment elevation (mm)	Rise in pulmonary artery diastolic pressure (mm Hg) (%)	ECG leads with maximum change	Painful test (+/-)	Spasm at angiography
1	+	100	+2.0	*	Anterior	+	LAD
2	+	100	+6.5	12.4 (117)	Anterior	+	LAD
3	-	200	0	8 (100)	—	+	RCA
4	-	1000	0	0	—	-	—
5	+	100	+1.5	1.5 (18.8)	Inferior	+	RCA

*Previous data without pulmonary artery diastolic pressure recording.
LAD/RCA, left anterior descending and right coronary arteries; ECG, electrocardiogram.

addition, they were asked to press the event marker so that the ST segment and pulmonary artery traces were marked.

EXERCISE TEST

Exercise testing was performed according to a modified Bruce protocol.⁹ Transducer tipped pulmonary artery pressure and frequency modulated electrocardiogram were recorded continuously. A 12 lead electrocardiogram was recorded on paper at one minute intervals. The exercise test was terminated by angina, dyspnoea, multiple ventricular extrasystoles, hypotension, ST segment depression or elevation >0.3 mV, or exhaustion.

At the end of the period of ambulatory monitoring the pulmonary artery catheter was removed and the pulmonary artery trace was replayed via a PB2 unit and PM3 amplifier. This was displayed on an SE laboratories 6008 oscillograph. The entire period of recording of the pulmonary artery diastolic pressure was displayed and measured on ultraviolet paper with a calibrated scale from a zero reference point. The pulmonary artery diastolic pressure was measured during both painful and painless episodes of ST segment depression on a beat to beat basis five minutes before the onset of the earliest change in pulmonary artery pressure and five minutes after the pulmonary artery diastolic pressure had returned to baseline. The pulmonary artery diastolic pressure was measured at the end of expiration.

STATISTICAL ANALYSIS

A change of at least three standard deviations from the mean level over a five minute period before any change in pulmonary artery pressure, heart rate, or ST segment was regarded as statistically significant. Wilcoxon rank sum testing was used for analysis.

Results

ERGOMETRINE MALEATE PROVOCATION

Four patients had angiographically confirmed coronary artery spasm after ergometrine maleate provocation. In patient 3 chest pain developed after a dose

of 200 μ g in the absence of ST segment changes and patient 4 was unaffected by a total dose of 1000 μ g. Patients 3 and 4 had spontaneous episodes of ST segment elevation. The haemodynamic response to ergometrine maleate was variable (table 2). Pulmonary artery diastolic pressure tended to rise (range 1.5–12.4 mm Hg (18.8–117%)). Patient 3 had no ST segment change despite a rise in pulmonary artery diastolic pressure of 8 mm Hg (100%). The most pronounced haemodynamic response to ergometrine maleate occurred in patient 2 (fig 1). A significant rise in pulmonary artery diastolic pressure occurred 102 seconds after the dose of 100 μ g; 42 seconds later the heart rate increased and 66 seconds later there was an abrupt rise in the ST segment. Pain occurred six seconds after the onset of ST segment elevation. The time to maximum pulmonary artery pressure was 220 seconds, maximum heart rate (145 beats/minute) 228 seconds, and maximum ST segment elevation 250 seconds. The episode of ST segment elevation was followed by ST segment depression and resolution of pain after isosorbide dinitrate.

EXERCISE TESTING

Patients 1–4 underwent treadmill testing (table 3). Three patients developed ST segment depression of >1 mm and one had ST elevation. In all cases there was a rise in pulmonary artery diastolic pressure. The greatest change in pulmonary artery diastolic pressure (12.4 mm Hg (775%)) occurred in the patient with ST segment elevation of 2.8 mm. This was the only patient in whom chest pain developed. There was a poor correlation between the magnitude and duration of ST segment change ($r = 0.16$, $p > 0.05$) but there was a closer relation between the magnitude and duration of pulmonary artery diastolic pressure ($r = 0.74$, $p < 0.05$). Duration of exercise correlated with the duration of elevation in pulmonary artery diastolic pressure ($r = 0.84$, $p < 0.05$). In patient 3, who had ST segment elevation, the onset of the change in the ST segment and rise in pulmonary artery diastolic pressure were simultaneous. In two of the other three patients with ST

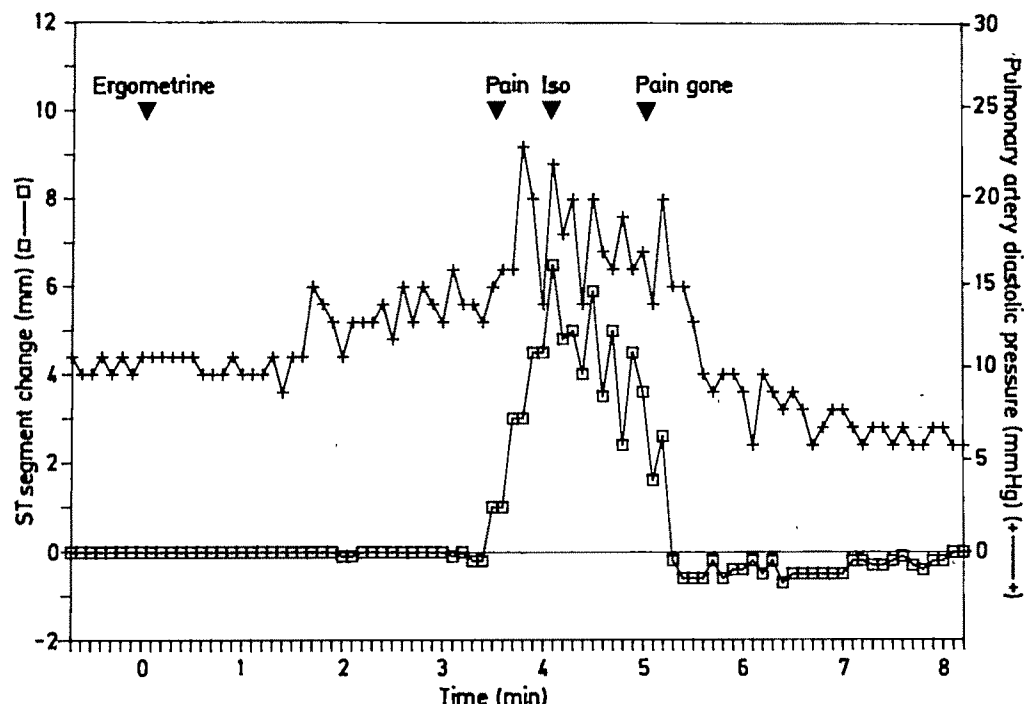


Fig 1 Haemodynamic and electrocardiographic response to a total dose of 100 μ g of ergometrine maleate in patient 2. A significant rise in pulmonary artery diastolic pressure occurred 102 seconds after the 100 μ g dose of ergometrine. Forty two seconds later the heart rate increased and 66 seconds later there was an abrupt rise in the ST segment. Pain occurred six seconds after the onset of ST segment elevation. The time to maximum pulmonary artery pressure was 220 seconds and to maximum ST segment elevation 250 seconds, and a maximum heart rate of 145 beats per minute occurred at 228 seconds. The episode of ST segment elevation was followed by ST segment depression and resolution of pain after isosorbide (Iso).

segment depression pulmonary artery diastolic pressure increased before ST segment change; the reverse occurred in the remaining patient. ST segment changes were maximal in lead CM5 in all four patients.

AMBULATORY EPISODES

Two hundred and seventy hours of ambulatory recording of pulmonary artery pressure and frequency modulated electrocardiogram were analysed and 20 episodes of ST segment change were noted.

Twelve of these were painful and the remainder were not. Figure 2 summarises the diurnal distribution of episodes. Most episodes occurred between 4 am and 8 am. Table 4 shows the number of episodes and the duration of ambulatory monitoring for each patient.

PAINFUL EPISODES

Eleven episodes were associated with ST segment elevation (median 2.15 mm, range 1–3.3) and one with 1 mm ST depression. Pain was a late feature in

Table 3 Response to treadmill exercise

Patient	Magnitude of ST segment response (mm)	Rise in pulmonary artery diastolic pressure (mm Hg) (%)	Pain (+/–)	Duration of exercise (min)	Duration of ST segment change (min)	Duration of raised pulmonary artery diastolic pressure (min)
1	–2.0	10 (77)	–	12.3	36.5	20.1
2	–1.6	5.4 (207)	–	13	2.6	13.5
3	+2.8	12.4 (775)	+	5.2	14.2	5.2
4	–2.1	3.5 (12)	–	9.5	11	9.2

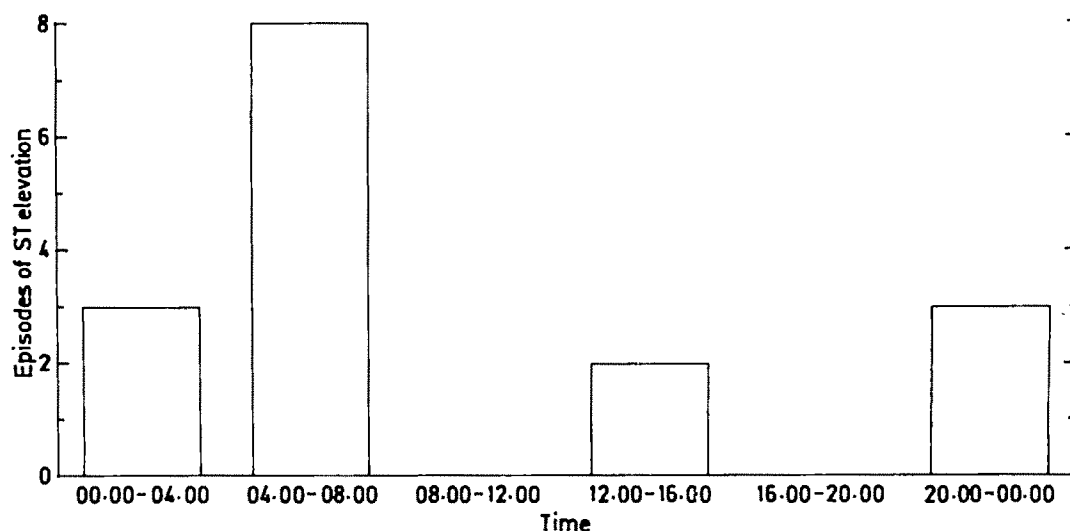


Fig 2 The diurnal distribution of episodes of ST segment elevation. Most episodes occurred in the early morning hours before waking.

nearly all cases, following the point of maximal ST segment elevation or depression. There was a rise in pulmonary artery diastolic pressure during six of the episodes of ST segment elevation. The onset of rise in pulmonary artery diastolic pressure was simultaneous with or followed the rise in the ST segment in all but one episode. Maximum pulmonary artery diastolic pressure and maximum ST segment elevation tended to coincide ($p < 0.05$). Ten of the eleven episodes of ST segment elevation occurred at rest. Glyceryl trinitrate was taken on one occasion and there was no change in pulmonary artery diastolic pressure. ST segment depression preceded or followed ST segment elevation in two episodes. Episodes of ST segment elevation not associated with a rise in pulmonary artery diastolic pressure were of shorter duration (median 1.15 minutes, range 0.6–2.6) than those episodes with a rise in pulmonary artery diastolic pressure (median 4.65 minutes, range 2–6). ST segment changes during different episodes usually occurred in the same territory in each patient.

PAINLESS EPISODES

Four episodes were associated with ST segment elevation (1.2–2.2 mm) and there was a rise in pulmonary artery diastolic pressure (66–344%) in three of these episodes that occurred simultaneously with or after the onset of ST segment elevation. There was no rise in pulmonary artery diastolic pressure in the remaining episode (patient 3) despite 27 minutes of ST segment elevation reaching a maximum of 2.2 mm. All episodes of ST segment elevation occurred at rest and one episode was followed by ST segment depression. ST segment elevation (median 1.25 minutes, range 0.8–27) lasted longer than the rise in pulmonary artery diastolic pressure (median 0.6 minutes, range 0.4–1) ($p < 0.05$). Four episodes of ST segment depression (1–1.2 mm) in the absence of ST segment elevation were recorded. All occurred on exertion and all were associated with a rise in pulmonary artery diastolic pressure (57–275%). The onset of rise in pulmonary artery diastolic pressure preceded the onset of ST segment depression in two episodes, followed it in one, and was simulta-

Table 4 Number of episodes of ST segment elevation during ambulatory monitoring

Patient	Ambulatory monitoring (h)	Daytime painful episodes	Daytime silent episodes	Nocturnal painful episodes	Nocturnal painless episodes	Total
1	120	0	1	0	0	1
2	48	0	2	0	0	2
3	30	3	3	0	0	6
4	48	4	2	4	0	10
5	24	0	0	0	0	0

neous with the remaining episode. The duration of a raised pulmonary artery diastolic pressure on exertion (median 1.95 minutes, range 1.8–2) was longer than that during episodes at rest (median 0.6 minutes, range 0.4–1) ($p < 0.05$).

Discussion

We examined the haemodynamic response to myocardial ischaemia in patients with variant angina by means of simultaneous ambulatory pulmonary artery pressure and ST segment monitoring. Previous studies have been limited to patients confined to bed in the coronary care unit and have used fluid filled catheter systems.^{2,3,5,10} The transducer tipped catheter technique used in this study is both accurate and allows for full ambulation.⁸ We have shown that changes in pulmonary artery diastolic pressure do not precede ST segment elevation in spontaneous variant angina and this confirms the results of previous studies.^{2,11,12}

Symptomatic and asymptomatic ST segment changes have been recorded by ambulatory monitoring¹³ and in the coronary care unit.² In our study episodes of symptomatic ST segment elevation were not always associated with a rise in pulmonary artery diastolic pressure. The presence or absence of a rise in pulmonary artery diastolic pressure was related to the duration of ST segment elevation in some patients. Pain was a late feature in most cases.^{14–17} In asymptomatic episodes there was a different haemodynamic response in those with ST segment elevation at rest and in episodes with exertional ST segment depression. The magnitude of pulmonary artery diastolic pressure increase was greatest on exertion.

It has been suggested that episodes of ST segment depression and ST segment elevation occurring within a few minutes of each other show similar haemodynamic patterns.^{2,17} The interpretation of the haemodynamic changes may be difficult when ST segment depression and elevation occur sequentially.

Episodes of ST segment elevation tend to occur in the early morning.^{12,18–20} Eleven of the 20 episodes occurred between 4 am and 8 am. Coronary artery tone may be increased at night and is highest in the early morning^{21,22}; however, it has also been shown that there is no increase in sympathetic activity to the heart before the onset of ST segment elevation.²³ Nocturnal ST segment elevation has been associated with rapid eye movement sleep or changes in sleep pattern²⁴ but others have refuted these findings.^{23,25} There is a diurnal variation in pulmonary artery diastolic pressure with a significant rise during the night with peak levels

being reached in the early morning hours.²⁶ This may be of importance because the raised left ventricular filling pressure in the early morning hours coincides with the largest number of episodes of ST segment elevation at rest.

Ergometrine maleate is an α adrenergic agonist that is used to assess the responsiveness of the coronary arteries to vasoconstrictor stimuli. This has been shown to be a highly specific test for coronary artery spasm in 90–100% of cases.¹² Ergometrine maleate increases left ventricular dimension, with resultant poor contractility,²⁷ and produces a dramatic reduction in coronary sinus flow consistent with an increase in coronary vascular resistance.^{28,29} We have shown that this test was positive in four of the five patients with variant angina. Patient 4 was totally unresponsive to a dose of 1000 μ g of ergometrine maleate and yet had documented spontaneous episodes of ST segment elevation on ambulatory monitoring. Patient 3 developed chest pain after 200 μ g of ergometrine maleate with no ST segment changes. One patient had a dramatic response to a total dose of 100 μ g of ergometrine maleate with ST segment elevation of 6.5 mm. As a group the change in pulmonary artery diastolic pressure was variable but the response in patient 2 (fig 1) showed that the rise in pulmonary artery diastolic pressure occurred before the heart rate and ST segment changes.

Pharmacological interference with ergometrine maleate may produce coronary artery spasm but appears to have a different haemodynamic effect from that seen during spontaneous episodes. A study in which a transducer tipped catheter was used showed a rise in left ventricular end diastolic pressure which preceded pain and ST segment elevation in a single patient after 330 μ g of ergometrine maleate.³⁰ Patient 1 had only one episode and patient 5 no episodes of ST segment elevation during studies lasting 120 and 48 hours respectively. Both of these patients had positive ergometrine maleate provocation tests with coronary artery spasm at angiography and previously documented episodes of ST segment elevation. Thus disease activity can vary such that patients may have multiple daily attacks for some time followed by a pain free interval of several weeks.

Exercise testing in untreated patients with acute variant angina has been shown to produce ST segment elevation in approximately 30% of cases, ST segment depression in 30%, and no significant change in the remainder. The ST segment response is not predictive of the presence of or the severity of underlying fixed coronary artery disease.³¹ Four of the five patients in our study performed an exercise test. Three had ST segment depression > 1.5 mm

with a rise in pulmonary artery diastolic pressure of 116–207% (3.5–10 mm Hg). This response to treadmill exercise was similar to that reported in a previous study of 15 patients with documented coronary artery disease and no documented spasm in whom there was a rise in pulmonary artery diastolic pressure (median 5 mm Hg, 69%; range 0–13.8 mm Hg, 0–262%). Only one patient in the latter group failed to have a rise in pulmonary artery diastolic pressure in the presence of important ST segment depression.⁷

ST segment depression during an exercise test has been shown to occur in different leads from those showing ST segment elevation at rest, suggesting that the same myocardial region may not be affected by ischaemia at rest and during exercise.^{18,32} In one patient (case 4) ST segment depression developed in lead CM5 and the anterior V leads during exercise whereas during several episodes at rest there was ST segment elevation in the inferior leads. Coronary arteriography in this patient showed irregularities in the left anterior descending and circumflex coronary arteries with a 50% stenosis in the proximal right coronary artery.

Various mechanisms for angina secondary to coronary spasm have been suggested since spasm was first suggested as a possible mechanism for angina pectoris.^{32,33} Angina has been described by Prinzmetal in patients with normal coronary arteries¹ but is more commonly associated with fixed coronary artery obstruction.²³ Only one patient in this study had normal coronary arteries.

Coronary blood flow measured by thermodilution techniques has been shown to fall during spontaneous variant angina.²⁹ A fall in coronary sinus oxygen saturation consistently precedes ST segment elevation, thus indicating that this factor has a causal role in the reduction in coronary blood flow.³ Myocardial scintigraphy with thallium-201^{14,34} and I-131 labelled microaggregated human serum albumin³⁵ has shown that transmural defects are present during ST segment elevation and absent in the resting state.

Some workers have shown that coronary artery spasm is a frequent cause of angina^{18,36} but Quyyumi *et al* noted that of 100 consecutive patients referred with chest pain for coronary arteriography, only two had ST segment elevation on ambulatory monitoring.³⁷ Our study was confined to five patients and has confirmed that ST segment elevation is infrequent and seldom, if ever, occurs other than in the resting state.

The technique of ambulatory pulmonary artery pressure monitoring has provided a means of studying left ventricular function in ambulant patients with variant angina. We have confirmed that

changes in pulmonary artery diastolic pressure, reflecting changes in left ventricular end diastolic pressure, do not precede the onset of ST segment elevation in most episodes of variant angina. The response is variable, however, when the changes are provoked by exercise testing or ergometrine maleate.

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The haemodynamic significance of asymptomatic ST segment depression assessed by ambulatory pulmonary artery pressure monitoring

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SUMMARY A transducer-tipped catheter with simultaneous frequency modulated electrocardiograms and a miniaturised tape recorder was used to record ambulatory pulmonary artery pressure for 24-48 hours in 19 men (mean age 57.7) with clinical and angiographic evidence of coronary artery disease. Sixty seven episodes of ST segment depression (>1 mm) were recorded. Thirty five were accompanied by pain of which six occurred at night; in 34 pulmonary artery diastolic pressure rose significantly. In all but two of the 32 episodes of painless ST segment depression (four of which were at night) there was a significant rise in pulmonary artery diastolic pressure. No such rise was found in six normal subjects during exertion. ST segment changes tended to occur before (24 episodes) or at the same time (27 episodes) as changes in pulmonary artery diastolic pressure. ST segment depression followed an increase in pulmonary artery diastolic pressure in only 13 episodes. The times to maximum ST depression and maximum pulmonary artery diastolic pressure rise were similar. Painful and painless ST segment depression could not be distinguished on the basis of the configuration of the ST segment or in terms of the changes in the pulmonary artery diastolic pressure.

Ambulatory electrocardiographic monitoring is now widely used in the evaluation of patients with coronary artery disease.^{1,2} During episodes of angina transient ST segment depression develops.^{3,4} Similar electrocardiographic changes may also occur in the absence of chest pain.⁵⁻⁷ In normal individuals ST segment changes unrelated to myocardial ischaemia may occur during exercise, but in patients with proven coronary artery disease the development of ST segment depression, particularly at low heart rates, is likely to indicate the presence of myocardial ischaemia.⁸⁻¹⁰ Measurements of the left ventricular end diastolic pressure or pulmonary artery pressure by fluid filled catheters in the coronary care unit or catheter laboratory have shown that left ventricular end diastolic pressure rises during myocardial ischaemia. This was also evident during silent ST segment depression, but the

changes were less pronounced than during symptomatic episodes.¹¹⁻¹³ No such investigations have been performed in ambulant patients, however. We have used ambulatory pulmonary artery pressure monitoring with a transducer tipped catheter to evaluate both painful and painless episodes of ST segment depression ischaemia in patients with coronary artery disease.¹⁴

Patients and methods

We studied 19 men (mean (SD) age 57.7 (11) years) with clinical and angiographic evidence of coronary artery disease. Nine had a previous myocardial infarction (8 inferior, 1 anterior). Fifteen had three vessel disease, two had two vessel disease, and one had single vessel disease. All had positive exercise tests and all patients had at least one episode of ST segment depression on ambulatory monitoring over a 24 hour period. In addition, a further six patients with chest pain, normal coronary arteries, and negative exercise tests were studied as controls.

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We excluded patients with evidence of heart failure, other forms of heart disease, and pulmonary vascular disease. All antianginal medication other than glyceryl trinitrate was discontinued at least 48 hours before the study and pulmonary artery pressure monitoring was performed for at least 24 hours, and where possible up to 48 hours. ST segment monitoring was performed throughout this period.

The study was approved by the hospital ethics committee and the patients gave their informed and written consent.

ST SEGMENT MONITORING

ST segment monitoring was monitored on a frequency modulated recorder and leads CM2 and CM5 were recorded.¹ The frequency modulated electrocardiogram was replayed on an Oxford MA20 scanner. Changes in the ST segment were measured 80 ms after the J point to an accuracy of 0.1 mm by means of a magnifying lens with graticule. Planar or downsloping ST segment depression of >1 mm lasting at least 30 seconds was regarded as important. The heart rate and ST segment changes were analysed on a beat to beat basis for five minutes before each episode and again up to five minutes after the ST segment had returned to basal levels.

PULMONARY ARTERY PRESSURE MONITORING

A polyurethane 6 French NIH type catheter with a miniature strain gauge transducer mounted on the tip was used.¹⁴ This was calibrated after immersion in saline for one hour before use. The catheter was introduced percutaneously via a subclavian vein to the main pulmonary artery under fluoroscopy. The transducer was driven and demodulated by an electrically isolated Gaeltec pre-amplifier. The pulmonary artery pressure was recorded on an Oxford Medilog 1 miniature recorder that had been modified by the insertion of an AM4 pressure module. The pulmonary artery recorder was linked to the frequency modulated electrocardiogram recording by an event button that marked both the frequency modulated electrocardiogram and the pulmonary artery trace.

At the end of 24 to 48 hours of recording the pulmonary artery catheter was removed and the pulmonary artery pressure was replayed via a PB2 unit and a PM3 amplifier. This was displayed on an SE Laboratories 6008 oscillograph. The entire period of recording of the pulmonary artery pressure was displayed on ultraviolet paper and measured with calibrated scale from a zero reference point. The pulmonary artery diastolic pressure was measured during both painful and painless episodes of ST segment depression on a beat to beat basis for five minutes before the onset of the earliest change in

pulmonary artery pressure and for five minutes after the pulmonary artery pressure had returned to baseline. In addition, any changes in pulmonary artery pressure not accompanied by ST segment changes were analysed in a similar manner. The pulmonary artery diastolic pressure was measured at the end of expiration to allow for respiratory variation.

ANGINA DIARY

Patients were instructed to keep diaries during the period of ambulatory pulmonary artery pressure and ST segment monitoring. They were asked to note the time of onset and severity of chest discomfort and their activity at the time of pain. In addition, they were asked to press the event marker so that both the ST segment and pulmonary artery trace were marked.

STATISTICAL ANALYSIS

A significant change in the basal ST segment, heart rate, or pulmonary artery diastolic pressure was taken to be a change of at least 3 SD from the mean level measured over five minutes before any change in the pulmonary artery pressure. Wilcoxon rank sum testing was used for analysis.

Results

Sixty seven episodes of ST segment depression (>1 mm) were recorded in the nineteen patients. Thirty five episodes were accompanied by pain and six of these occurred at night. In all but one of the episodes of ST segment depression accompanied by chest pain there was a significant increase in pulmonary artery diastolic pressure. There were thirty two episodes of ST depression that were not accompanied by chest pain and four of these occurred during the night; in only two was no significant increase in pulmonary artery diastolic pressure found. Most episodes were maximal in lead CM5.

There were 31 episodes in which there was a significant increase in pulmonary artery diastolic pressure without ST segment depression of ≥ 1 mm. In 20 of these episodes a minor (<1 mm) change in the ST segment was recorded, but in 11 episodes no alteration in the ST segment was seen. There was no relation between the severity of ST segment change and the size of the increase in pulmonary artery diastolic pressure (table 1). The relation between the time of onset of ST segment depression and the onset of changes in pulmonary artery diastolic pressure was variable, although ST segment changes tended to occur before or at the same time as changes in pulmonary artery diastolic pressure ($p < 0.01$). The onset of ST segment depression preceded the earliest change in pulmonary artery diastolic pres-

Table 1 *Relation between the magnitude of ST segment depression and pulmonary artery diastolic pressure during painful and silent episodes of myocardial ischaemia*

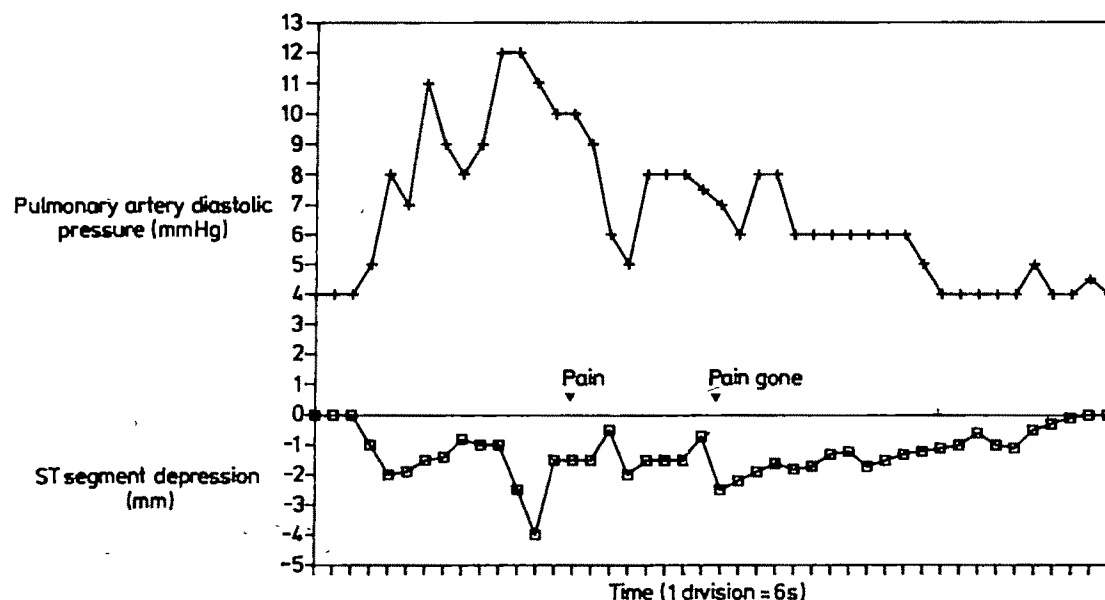
ST segment depression (mm)			Daytime painful	Daytime painless	Nocturnal painful	Nocturnal painless
0	Increase in PADP (median (range)):	%	70 (36-85)	125 (77-216)	23 (23)	132 (114-150)
		mm Hg	5.2 (3.2-11)	11.1 (7-13)	5 (5)	8.5 (8-9)
	No of episodes		3	3	1	2
0-1	Increase in PADP (median (range)):	%	67 (50-97)	61 (30-105)	35 (35)	44 (44)
		mm Hg	7 (4-10)	5.2 (2.5-12.3)	3 (3)	8 (8)
	No of episodes		10	10	1	1
1-2	Increase in PADP (median (range)):	%	73 (23-135)	66 (0-200)	56 (0-108)	14 (0-39)
		mm Hg	7.4 (1.8-11.9)	4.7 (0-12.3)	5 (0-6.5)	2.2 (0-3.5)
	No of episodes		19	23	4	3
>2	Increase in PADP (median (range)):	%	108 (23-237)	54 (12-140)	51 (44-57)	100 (100)
		mm Hg	8.3 (2-19.7)	7 (1.5-14.6)	4 (4)	3 (3)
	No of episodes		10	5	2	1

PADP, pulmonary artery diastolic pressure.

Table 2 *Pulmonary artery diastolic pressure changes during ST segment depression*

		Daytime painful	Daytime painless	Nocturnal painful	Nocturnal painless
No of episodes		29	28	6	4
ST segment depression (median (range) (mm))		1.5 (1-4)	1.4 (1-3.2)	1.5 (1-2.8)	1.4 (1-2.3)
Increase in PADP (median (range)):	%	87.5 (20-237)	66 (0-200)	53 (0-108)	26 (0-200)
	mm Hg	7.5 (1.8-19.7)	4.9 (0-14.6)	4.5 (0-6.5)	2.6 (0-3.5)
PADP before each episode (median (range) (mm Hg))		8.2 (4-18)	8.3 (2-15.3)	9.5 (7-18)	7 (3-18)

PADP, pulmonary artery diastolic pressure.

Figure *Changes in pulmonary artery diastolic pressure and the ST segment during an episode of myocardial ischaemia.*

sure in 24 episodes. In a further 27 episodes the pulmonary artery diastolic pressure and ST segment changes occurred simultaneously. ST segment depression followed an increase in pulmonary artery diastolic pressure in only 13 episodes.

There were no acute changes in pulmonary artery diastolic pressure during ambulatory monitoring in the six control subjects. When they were exercised the median increase in pulmonary artery diastolic pressure was 0 mm Hg (range 0–3). This increase in pulmonary artery systolic pressure was similar to that recorded in patients with coronary artery disease.

PAINFUL VERSUS PAINLESS EPISODES

The magnitude of ST segment depression was similar in episodes that occurred with or without chest pain and in episodes that occurred during the day or at night ($p < 0.05$) (table 1). Increases in pulmonary artery diastolic pressure were also similar during episodes of painful and painless nocturnal and daytime ST segment depression. The basal pulmonary artery diastolic pressure in the five minutes before the onset of ST segment changes was no different in painful and painless episodes of ST segment depression whether or not they occurred during the day or at night (table 2). The maximum pulmonary artery diastolic pressure tended to coincide with the point of maximum ST segment depression and both of these preceded the complaints of chest pain (fig).

Discussion

There is considerable interest in the significance of silent myocardial ischaemia.^{4 12 15} While prognostic information and the therapeutic implications of painless ST segment changes is still under investigation,^{16 17} previous studies of left ventricular function measured in the coronary care unit have shown that left ventricular end diastolic pressure rises during painless myocardial ischaemia.¹¹ In this study of ambulant patients we have shown that transient abnormalities of left ventricular functions, as reflected by alterations in pulmonary artery diastolic pressure, do occur during painful and painless episodes of ST segment depression. In 1958 Müller and Rørvik first saw an abnormal increase in pulmonary artery pressure in two patients with spontaneous angina.¹⁸ Other studies have confirmed these observations.^{19–21} In the absence of pulmonary vascular disease and mitral valve obstruction, the pulmonary artery diastolic pressure correlates well with left ventricular pressure.^{14 22} We have used this relation to develop a technique to record the pulmonary artery pressure in ambulant patients.¹⁴ This

has permitted the significance of symptomatic and asymptomatic ST segment changes to be examined in ambulant patients. The introduction of a cardiac catheter into the left ventricle or pulmonary artery with recordings made in the coronary care unit or catheter laboratory does not permit normal physiology to be studied and considerable caution is necessary in interpreting the findings of such studies in painless ischaemia.

Several studies have shown that only about 30% of episodes of ST segment depression that occur in patients with angina pectoris during 24 hour ambulatory monitoring are accompanied by chest pain.^{12 23 24} Examination by positron tomography has confirmed that painless episodes of ST segment depression are accompanied by myocardial ischaemia detected by abnormal uptake of rubidium-82.^{25–27} We found that each episode of ST segment depression was accompanied by an increase in pulmonary artery diastolic pressure. The extent of this increase varied from episode to episode even within the same patient, but in general both painful and painless episodes of ST segment depression were accompanied by similar increases in pulmonary artery diastolic pressure. Furthermore, the increase in pulmonary artery diastolic pressure was independent of the magnitude of ST segment depression recorded on ambulatory monitoring. Indeed, when only a minor change in the ST segment was seen it was still possible for there to be a large increase in pulmonary artery diastolic pressure. It is impossible to assess the full extent of ST segment changes in only two electrocardiographic channels. There was no alteration in pulmonary artery diastolic pressure in the control subjects during ambulatory monitoring or treadmill exercise.

We cannot be certain that the patient pressed the event button at the same time as the onset of chest pain. The timing of the onset of ST segment change, rise in pulmonary artery diastolic pressure, and the patient's awareness of the development of chest pain must be interpreted with caution.^{28 29} The sequence of events was similar, however, to that described in previous catheterisation studies^{6 12 13 30} in which the ST segment changes usually preceded changes in pulmonary artery diastolic pressure and both occurred before the patient complained of chest pain.

Our finding that symptomatic and silent episodes of ST segment depression are associated with considerable alterations in left ventricular function is similar to previous reports.¹¹ Because patients took glyceryl trinitrate we were unable to compare the duration of rise in pulmonary artery diastolic pressure during silent and symptomatic episodes of ST segment depression.

In conclusion, episodes of painful and painless ST segment depression are associated with similar haemodynamic changes. The prognostic and therapeutic implications of these findings need to be explored.

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Mechanism of the dicrotic pulse

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SUMMARY The dicrotic pulse is an abnormal carotid pulse found in conjunction with certain conditions characterised by low cardiac output. It is distinguished by two palpable pulsations, the second of which is diastolic and immediately follows the second heart sound. In the course of open chest canine studies of the second heart sound, micromanometers and an electromagnetic flow meter were used to study proximal aortic haemodynamic function in both strong and weak beats. It was found that the incisural notch of the aortic pressure signal is not strongly dependent on the extent of left ventricular ejection, and is of essentially normal amplitude even in beats having greatly reduced aortic flow. In contrast, the magnitude of the systolic upstroke of the aortic pressure pulse is strongly determined by the magnitude of left ventricular ejection and is considerably reduced in weak beats. With low cardiac output the relative size of the incisural notch becomes exaggerated in comparison with the overall pulsation, thus creating the characteristic M shaped waveform of the dicrotic pulse.

The dicrotic pulse has long been described as a physical sign associated with low cardiac output.¹ As early as 1863, with the development of Marey's sphygmograph, the abnormality was documented graphically. This abnormal pulsation is characterised by the presence of two distinct upstrokes, the second being diastolic and immediately following the second heart sound. This configuration is shown in fig 1. Flemming suggested in 1881 that the necessary conditions for the abnormality included a fast pulse, elastic vessels, feeble tension in the vessels, and a small amount of blood injected with each ventricular systole.² In 1902, MacKenzie pointed out that dicrotism is usually present in conditions of weak ventricular contraction and relaxed vessels.³ Dicrotism has also been found in association with cardiomyopathy.^{4,5} In a more recent paper from this laboratory, Orchard and Craige reported that persistence of the dicrotic pulse is an important prognostic sign after open heart surgery.⁶

The mechanism of the dicrotic pulse has been the subject of debate. The importance of a competent aortic valve was suggested by the study of Orchard and Craige in which two of their patients lost ini-

tially large dicrotic waves when a paravalvar aortic leak developed.⁶ The contractile state of the myocardium is also of fundamental importance. Orchard and Craige reported that in pulsus alternans it is the weaker beats that display the dicrotic pulse more prominently. Some have suggested that dicrotism is a distortion of the waveform resulting from abnormal arterial resistance such that the dicrotic wave becomes exaggerated.⁴

As a part of open chest canine studies designed to study the second heart sound, we have made observations which we feel explain the genesis of this phenomenon.

Methods

Six mongrel dogs weighing from 20 to 35 kg were anaesthetised with intravenous pentobarbitone sodium and ventilated by means of a mechanical respirator. The dogs were placed in the supine position and a median sternotomy was performed. The pericardium was opened and sewn so as to create a pericardial cradle for the heart. The proximal aortic root was exposed by blunt dissection. An electromagnetic flow probe of the cuff type (Carolina Medical Electronics) was placed around the proximal aortic root, just above the coronary sinus. The flow signal was recorded on a direct current input channel of a multichannel physiological recorder (Electronics for Medicine VR12) with a bandwidth of

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120 Hz. The aortic and ventricular pressure signals were detected through high fidelity micromanometer tipped catheters (Millar Instruments). The aortic catheter was inserted through the right external carotid artery, with its micromanometer tip positioned within 2 cm of the aortic valve. The ventricular catheter was inserted directly through the left ventricular wall at the apex and positioned in the apical region of the ventricular chamber. The aortic and left ventricular pressure signals were recorded with a frequency bandwidth of 250 Hz. In some cases the aortic pressure signal was also recorded with a bandwidth of 25 Hz, and this low fidelity signal is shown simultaneously with the high fidelity aortic pressure signal in figs 2, 3, and 4. The high and low fidelity aortic pressure tracings were obtained from the same micromanometer tipped

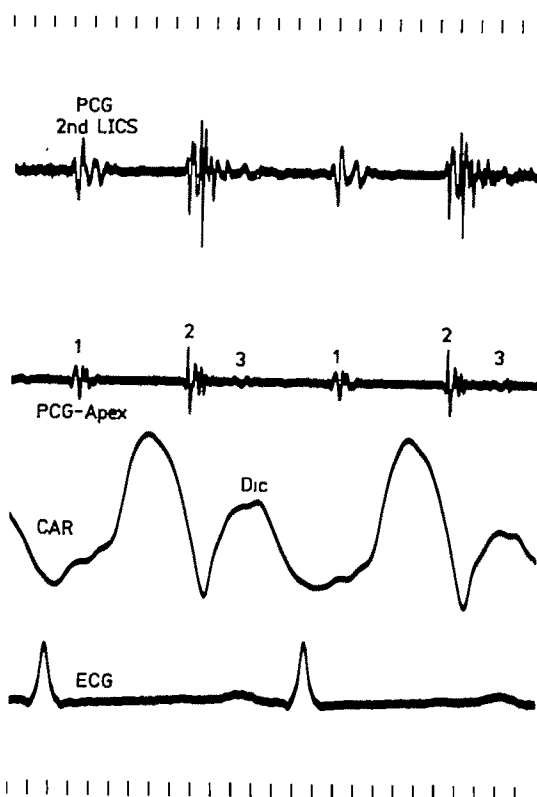


Fig 1 Recording of the carotid pulse and simultaneous phonocardiograms obtained from a patient with dilated cardiomyopathy in the non-invasive cardiac graphics laboratory. The carotid tracing shows a diastolic pulse with its distinguishing M shaped configuration of which the second component is diastolic. PCG 2nd LICS, phonocardiogram from second left intercostal space; PCG-Apex, phonocardiogram from apex; CAR, carotid tracing; Dic, the diastolic wave; ECG, the electrocardiogram.

catheter. In the recordings made during studies of haemodynamic failure, the high fidelity aortic and ventricular pressure signals are calibrated, as indicated in figs 3 and 4. In contrast, the low fidelity aortic pressure signal is not calibrated and is adjusted between recordings so as to show a pulsation of approximately constant amplitude. The recordings were made during control conditions and during heart failure subsequent to global hypoxaemia caused by interruption of the mechanical respirator.

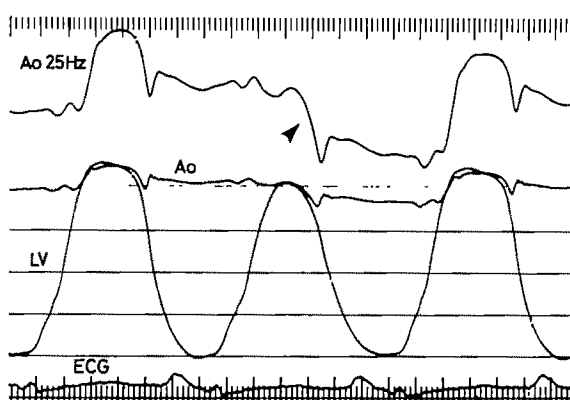


Fig 2 Recording obtained from open chest canine study during pulsus alternans. The weak beat shows no diminution of its incisural downstroke (arrow) and rebound, although its systolic upstroke is markedly diminished. Ao 25 Hz, low fidelity aortic pressure signal; Ao, high fidelity aortic pressure signal; LV, left ventricular pressure, ECG, electrocardiogram.

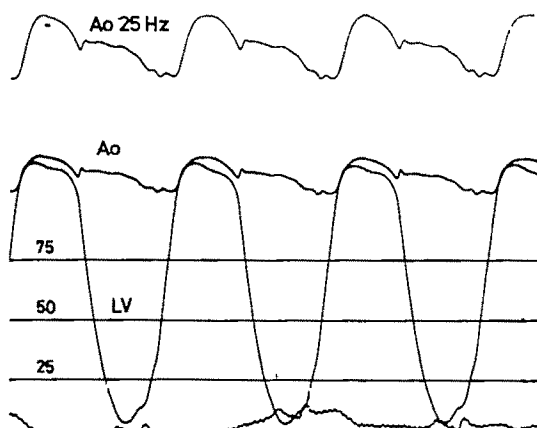


Fig 3 Recording obtained from open chest canine study during control condition. The aortic pressure waveform morphology is normal. Ao 25 Hz, low fidelity uncalibrated aortic pressure signal; Ao, high fidelity calibrated aortic pressure signal; LV, left ventricular pressure.

Results

Three of the dogs showed pulsus alternans, with alternating strong and weak beats. In addition, the weak beats showed slight alteration of strength, with some beats exceeding aortic pressure and others not exceeding aortic pressure. This fortuitous variation afforded an "experiment of nature" in which the incisural notch could be studied. An example is shown in fig 5. This figure shows a sequence of three weak beats numbered 1, 2, and 3. These numbered beats are shown to increase in strength, with beat number 2 being larger than number 1, and number 3

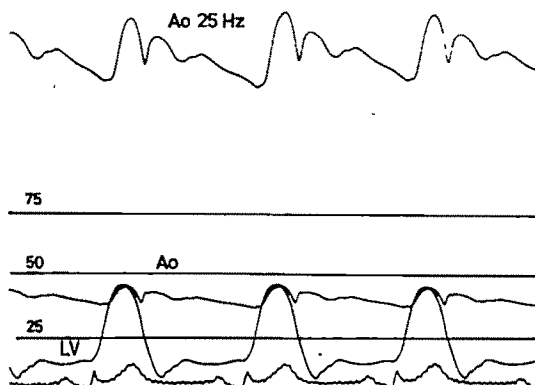


Fig 4 Recording obtained from same dog as in fig 3, now with heart failure. The low fidelity uncalibrated aortic pressure signal (*Ao* 25 Hz) now shows dicrotism. *Ao*, high fidelity calibrated aortic pressure signal; *LV*, left ventricular pressure.

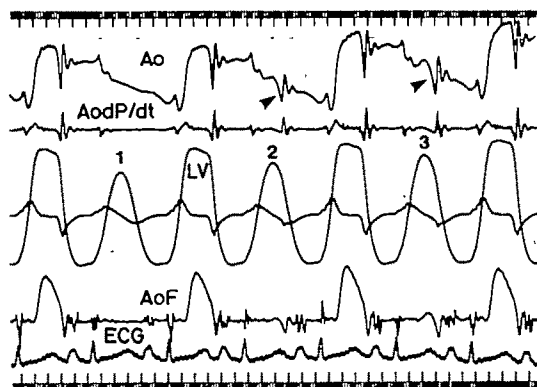


Fig 5 Recording obtained from open chest canine study during pulsus alternans. Weak beats numbered 1, 2, and 3 grow progressively in peak systolic pressure. Weak beats 2 and 3 result in incisural notches of the aortic pressure signal (arrows). *Ao*, high fidelity aortic pressure signal; *Ao dP/dt*, time derivative of aortic pressure; *LV*, left ventricular pressure; *AoF*, proximal aortic blood flow; *ECG*, electrocardiogram.

larger than number 2. In weak beat number 1 no aortic pressure pulse is produced. Therefore, the aortic pressure of beat number 1 shows no incisural downslope or rebound. During this beat there is no forward or retrograde proximal aortic flow seen in the flow signal. In weak beat number 2 an incisural downslope (arrow) and rebound is clearly demonstrated, even though essentially no forward aortic blood flow was detected in the flow signal. In weak beat number 3 the size of the incisural notch (arrow) is almost as large as that of the strong beats of the figure, even though the systolic upstroke of the pulsation is insignificant. Note also that the extent of retrograde aortic blood flow is as large in weak beat number 3 as it is in the strong beats, even though the extent of forward systolic blood flow is a very small percentage of that obtained in the strong beats.

Figure 2 shows simultaneously the high and low fidelity aortic pressure signals in a sequence that includes a weak beat due to pulsus alternans. The weak beat is characterised by a considerable reduction in the size of the overall aortic pressure pulse. The size of the incisural downslope (arrow) and rebound is, however, of the same size as that of the strong beats, again indicating the insensitivity of the magnitude of the incisural notch to the strength of systole.

Figures 3 and 4 were recorded from the same dog and indicate the characteristic alteration in the aortic pressure signal from the proximal aorta which we observed when the dogs experienced haemodynamic failure. Figure 3 shows the control condition, in which the aortic pressure signals display normal configuration. The incisural downslope and rebound are a small percentage of the overall pressure pulsation. Figure 4 shows the results obtained during haemodynamic failure. The overall aortic pressure pulse indicated in the calibrated high fidelity aortic pressure signal has reduced to approximately 60% of its size in fig 3. The size of the incisural notch, however, is essentially unchanged compared with that of fig 3. The amplifier gain of the low fidelity aortic pressure signal in fig 4 has been increased between recordings so that the size of the overall pulsation appears as large as in fig 3. When this is done, the low fidelity aortic pressure signal displays the characteristic dicrotic pulse waveform.

Discussion

In recording the carotid or other peripheral arterial pulsations in the non-invasive cardiac graphics laboratory it is widespread practice to adjust the amplifier gain of the recording equipment so as to obtain a tracing of convenient amplitude. This means that the smaller pulse associated with hae-

mododynamic failure is routinely recorded with larger gain than is the normal pulse. This practice is appropriate in that no attempt is usually made to quantify the pulse, and it is the waveform configuration and timing that are of principal concern. We therefore include in our tracings a low fidelity uncalibrated aortic pressure signal for which we adjusted the amplifier gain between recordings as the dog developed haemodynamic failure. There are obvious differences between this low fidelity filtered proximal aortic pressure signal and the non-invasively obtained carotid pulse. One important difference is that this signal obtained from the proximal aorta is not subject to the distortion that occurs as the pulse travels down the arterial tree. Our purpose for including the low fidelity pressure signal is to demonstrate that the characteristic dicrotic wave configuration can be detected in the proximal aorta and is not dependent on modification of the pulse as it travels to the peripheral circulation.

It should be noted that the configuration of the arterial pulse is not dependent on the actual magnitudes of its various components but instead is determined by the relative contributions of these. We hypothesise that the development of dicrotism, which appears to involve an increase in amplitude of the dicrotic wave component, is not actually the result of an exaggeration of the dicrotic wave but rather of a reduction of the systolic upstroke of the pulsation in conjunction with an essentially normal amplitude of the incisural downslope and rebound. This results in the characteristic M shaped configuration.

The ability to palpate the secondary component of the dicrotic pulse appears to be a consequence of the characteristics of the tactile sense. If two pulsations occurring closely in time are applied to the fingers, the ability to detect the second pulsation depends to a large extent on the relative amplitudes of the two pulsations. If the first pulsation is much more prominent than the second, the secondary pulsation will not be perceived. If the amplitude of the first pul-

sation is then reduced so as to more nearly equal the amplitude of the second pulsation, the second pulsation can be palpated even though it has not changed in amplitude. The auscultatory analogue of this phenomenon is well known, in that a loud sound or murmur may interfere with the appreciation of an immediately following softer event.

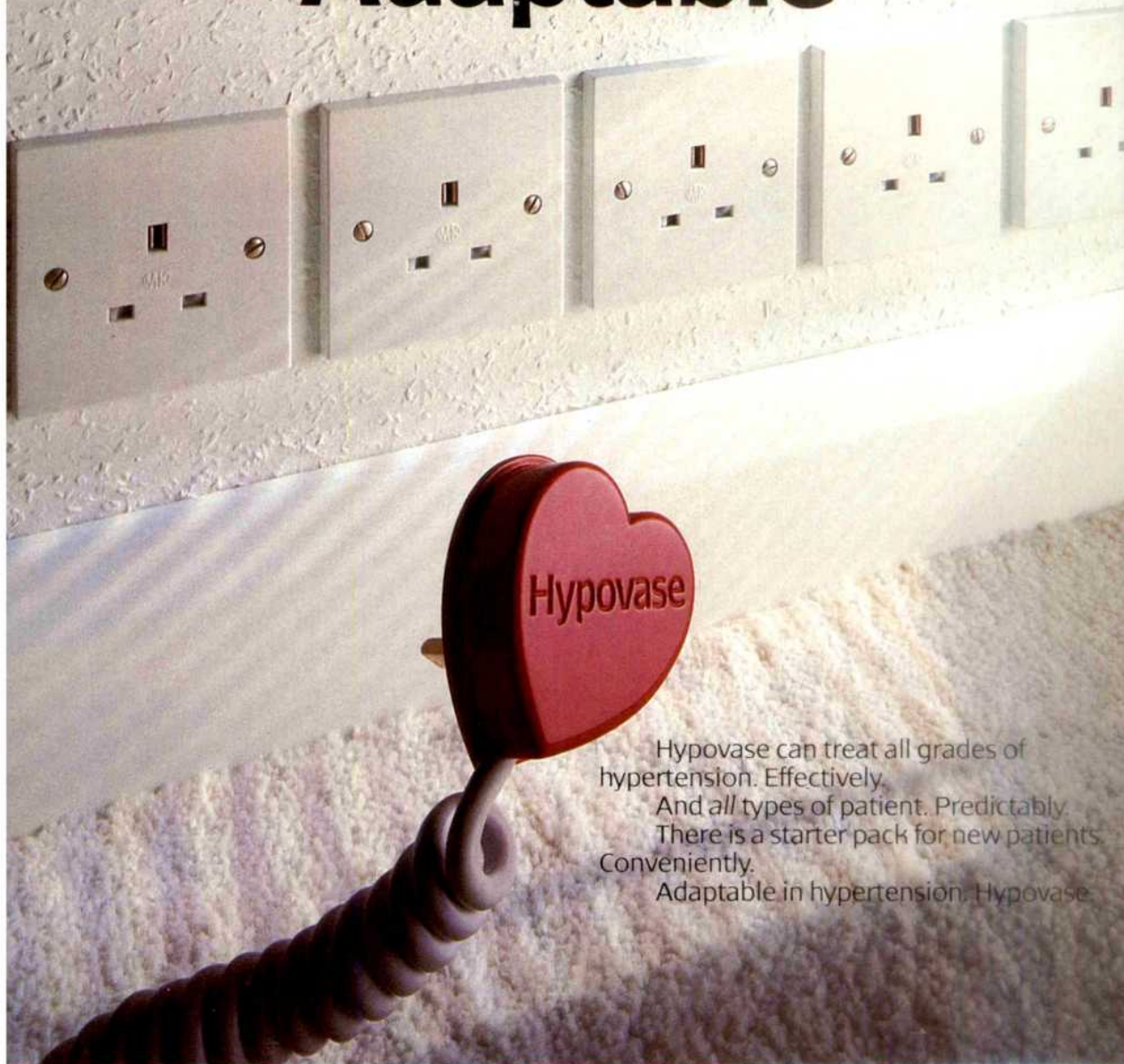
Conclusion

Whereas in the past cardiologists have interpreted the dicrotic pulse as the result of an exaggeration of the dicrotic wave, the actual basis for the unusual waveform appears to be a reduction of the overall pressure pulse in conjunction with an essentially normal magnitude of the incisural downslope and rebound. This causes the pulse to show a considerable increase in the relative contribution from the incisura, resulting in the characteristic M shaped waveform. Although we cannot exclude an additional involvement of transmission distortion as the pulse travels peripherally, we have demonstrated that the characteristic waveform of dicrotism can be detected in the proximal aorta immediately above the aortic valve.

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Tricuspid atresia in adolescents and adults: current state and late complications

CAROLE A WARNES, JANE SOMERVILLE

From the Paediatric and Adolescent Unit, National Heart Hospital, London

SUMMARY Twenty nine patients aged 15-35 years (mean 23) with tricuspid atresia and normally related great arteries were studied; 20 are alive. Ten patients who had had a Fontan operation (group 1) were compared with 10 patients with palliative shunts (9) or no surgery (1) (group 2). Patients were graded according to their ability to lead a normal life (ability index). Patients in group 1 tended to have a better ability index, a greater exercise capacity, and fewer social and extracardiac problems than those in group 2. The mean left ventricular ejection fraction measured by radionuclide angiography was the same in both groups. Arrhythmias were equally common in both groups; they appear to be age related and they occur independently of left ventricular function.

Increasing numbers of patients with tricuspid atresia are surviving to adolescence and adult life as a result of early palliative and reparative operations. Information about the late results is scarce and little is known of the medical and social problems that these patients encounter in adulthood. We have reviewed all patients with tricuspid atresia and normally related great arteries who attended the National Heart Hospital since 1965 and who survived beyond their fourteenth birthday. Procedures used for the management of complex heart disease are constantly changing and the survival of many of these adults is the result of pioneering efforts. We have examined the ability of such patients to lead a normal life in the long term.

Patients and methods

In 1985-86 we reviewed all patients with tricuspid atresia and normally related great arteries attending the National Heart Hospital since 1965 who survived to their fourteenth birthday. Patients were referred with complex problems from many centres and they represent a highly selected group. In all of them the diagnosis was confirmed by invasive

investigation. In four cases a necropsy was performed. Twenty of the 29 patients (16 men) aged 16-35 years (mean 23) are alive and all except one attended for review. The records of the nine patients who died were scrutinised and the cause of death was determined.

Nineteen of the 20 survivors seen in 1985-86 had clinical examination, chest x ray, electrocardiogram, 24-48 hour ambulatory monitoring, symptom limited exercise test by the modified Bruce protocol, and cross sectional echocardiography. Left ventricular function was also assessed with equilibrium electrocardiogram gated radionuclide angiography.

We assessed the patient's ability to lead a normal life according to the index shown in fig 1. We paid particular attention to difficulties with employment,

Ability index	
Grade 1	— Normal life Full time work or school Can manage pregnancy
Grade 2	— Able to do part time work Life modified by symptoms
Grade 3	— Unable to work Noticeable limitation of activities
Grade 4	— Extreme limitation Dependent Almost housebound

Fig 1 Ability index classification.

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Table 1 Summary of clinical data on 15 patients with tricuspid atresia and a Fontan operation

Case No	Age reached (yr)	Sex	Operations before Fontan operation and Age (yr)	Age at Fontan (yr)	Ability index	Rhythm problems	LVEF (%)
<i>Alive:</i>							
1	35	F	None	22	2	None	37
2	26	M	Blalock-Taussig shunt 4 Waterston shunt 8	12	2	A-V dissociation	42
3	24	M	Blalock-Taussig shunt 4	15	1	None	30
4	23	M	Glenn anastomosis 2/12 Blalock-Taussig shunt 12	21	2	None	51
5	23	F	Blalock-Taussig shunt 18 Glenn anastomosis 2/12	11	3	Atrial tachycardia	56
6	21	F	Glenn anastomosis 8/12 Blalock-Taussig shunt 8	12	2	Ventricular tachycardia	51
7	20	M	Blalock-Taussig shunt 8 Glenn anastomosis 4/12	9	2	Multiple APCs	35
8	20	M	Blalock-Taussig shunt 5 Blalock-Taussig shunt 1	17 16	2	None	70
9	18	M	Waterston shunt 5 Waterston shunt and Blalock-Hanlon 9/12	16	2	None	39
10	16	F	None	11	2	None	48
<i>Dead:</i>							
11	25	M	Blalock-Taussig shunt 4 Waterston shunt 21	25	Cause of death Sepsis		
12	22	F	Blalock-Taussig shunt 1 Glenn anastomosis 10 Potts shunt 17	22	Poor left ventricular function, raised pulmonary artery pressure		
13	22	F	Blalock-Taussig shunt 5 Waterston shunt 14	22	Sudden		
14	17	F	Blalock-Taussig shunt 2/12 Blalock-Taussig shunt 2	17	Atrial arrhythmias, left ventricular failure		
15	15	F	Blalock-Taussig shunt 7/12	15	Postoperative hypoxia		

APCs, atrial premature complexes; A-V, atrioventricular; LVEF, left ventricular ejection fraction.

education, training, contraception, and marriage, and whether the patient had been successful in obtaining a driving licence and life insurance.

We divided the patients into two groups; group 1 comprised 15 patients with Fontan's operation, and group 2, 14 patients with previous shunts or Glenn anastomoses including one woman aged 32 years who had not had operation. Tables 1 and 2 summarise the clinical data.

Results

GROUP 1: PATIENTS WITH A FONTAN OPERATION

Fifteen patients had had a Fontan operation at age 9–25 years (mean 16) (table 1). All except two (cases 1 and 10) had had one or more previous shunts or a Glenn anastomosis. Three patients (cases 9, 14, and 15) had had an arteriopulmonary shunt and four (cases 4, 5, 6, and 7) had had a Glenn anastomosis in infancy (< 1 year). Two patients (cases 4 and 12) had had three previous shunts. Two patients (cases 1 and 7) have small residual atrial septal defects and one patient (case 8) has a residual ventricular septal defect.

Mortality

Five patients died one day to one year after the Fon-

tan operation. Three died in the early postoperative period. A fourth (case 11) died six months later of uncontrolled sepsis after a reoperation for an open atrial septal defect. A woman of 22 (case 13) died unexpectedly after a bout of vomiting a year after an apparently successful Fontan operation (ability index 2). Postoperative angiography at six months had shown that the pulmonary vascular resistance was slightly increased as a result of the previous Waterston shunt. Necropsy showed that the unvalved conduit between right atrium and right ventricle was open, but it was lined with intimal peel.

Reoperation

Two of the 15 patients required late reoperation 10 years after the original Fontan procedure because of obstruction of the Dacron conduit connecting the right atrium to the pulmonary arteries. The conduit was replaced with an aortic valve homograft. Both patients had a functioning Glenn anastomosis which masked the conduit obstruction until they presented with presyncope. In both of them left ventricular function has deteriorated since reoperation. One (case 7) has angina that is probably associated with large acquired mediastinal coronary-bronchial collaterals causing a steal phenomenon (fig 2). The other (case 5) has congestion and a low cardiac out-

Table 2 Summary of clinical data on 14 patients with tricuspid atresia who had palliative shunts or no surgery

Case No	Age reached (yr)	Sex	Operations performed and age (yr)	Ability index	Rhythm problems	LVEF (%)	
Alive:							
16	35	M	Blalock-Taussig shunt	6	1	A-V dissociation, sinus arrest	69
17	32	F	Waterston shunt	22	3	Atrial tachycardia	32
18	30	F	None	18/12	3	Atrial fibrillation, paced	49
19	28	M	Aortopulmonary shunt	21	4	None	32
20	24	M	Glenn anastomosis	3/12	2	PVCs	45
			Potts anastomosis	6/12			
21	23	M	Glenn anastomosis	14	2	None	66
22	22	M	Blalock-Taussig shunt	10	2	None	38
			Blalock-Taussig shunt	19			
23	21	M	Blalock-Taussig shunt	2	1	Multiple APCs	36
24	18	M	Glenn anastomosis	2	2	APCs, coupled PVCs	No information
			Blalock-Taussig shunt	13			
25	18	F	Glenn anastomosis	2/12	2	No information	No information
Dead:							
26	30	F	Aortopulmonary shunt	22	Cause of death		
27	19	M	Glenn anastomosis	6/12	No information		
			Blalock-Taussig shunt	8	PH, grade 3/4 AR, shunts patent.		
28	18	M	Blalock-Taussig shunt	2/12	Failure, died suddenly		
			Glenn anastomosis	4/12	Thrombosed pulmonary arteries		
			Aorto-pulmonary shunt	11			
			Blalock-Taussig shunt	18			
29	17	F	Waterston shunt	2/12	Left ventricular and renal failure		
			Blalock-Taussig shunt	7	Died at transplant		

APCs, atrial premature complexes; AR, aortic regurgitation; A-V, atrioventricular; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension; PVCs, premature ventricular complexes.

put (ability index 3) related to a residual ventricular septal defect and a right ventricular-pulmonary artery connection; pulmonary artery pressure is raised (23 mm Hg systolic). It is hoped that ligation of the proximal pulmonary artery will reduce the pulmonary artery pressure.

Arrhythmias

Arrhythmias developed in four patients; in all of them they started after 20 years of age. Three have symptoms (cases 2, 5, and 6). In case 2 recurrent supraventricular tachycardia is controlled by amiodarone; this patient leads a normal life despite the intermittent atrioventricular dissociation that is shown by ambulatory monitoring. One patient (case 5) has non-sustained multifocal atrial tachycardia if she forgets to take a diuretic. In patient 6 non-sustained ventricular tachycardia developed at 20 years, eight years after her Fontan operation; this has responded to phenytoin. One other patient (case 7) has asymptomatic non-sustained multifocal atrial tachycardia. There was no apparent correlation between left ventricular dysfunction and the presence or onset of arrhythmias (fig 3).

The other six surviving patients, aged 16–35 years, are in sinus rhythm.

Functional status of survivors

Nine of the 10 survivors with Fontan procedures

aged 16–35 years (mean 23) remain well and acyanotic. One (case 1) has a residual atrial septal defect and cyanosis. Figure 4 shows the postoperative changes in ability index of each patient. Nine patients are currently leading nearly normal lives. Figure 5 shows their exercise capacity and ability index. One patient (case 1) was limited to stage I because of obesity and pain from a previous deep vein thrombosis that occurred after the Fontan operation. Four patients were limited to stage II.

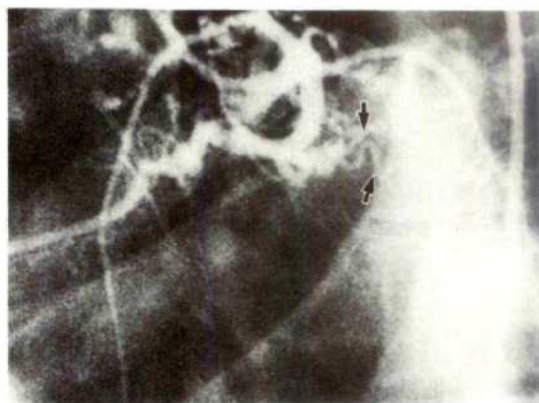


Fig 2 Injection into the left coronary system in case 7. There are multiple coronary collaterals (arrows) arising from the left circumflex coronary artery.

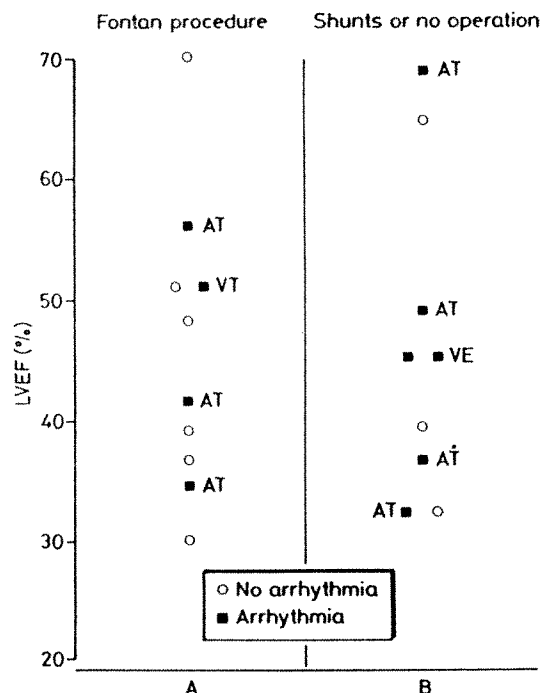


Fig 3 Left ventricular ejection fraction (LVEF) measured by radionuclide angiography of 10 patients with a Fontan operation and nine patients with palliative shunts or no surgery. There is no correlation between the presence of arrhythmias and LVEF. AT, atrial tachycardia; VE, frequent ventricular ectopic impulses; VT, ventricular tachycardia.

There was no correlation between exercise capacity and ability index.

Measured left ventricular ejection fraction (table 1) ranged from 30% to 70% (mean 46) and did not correlate with exercise capacity (fig 6) or ability indices (fig 7). Patients in whom arteriopulmonary shunts had been inserted during infancy (cases 8 and 9) did not have worse left ventricular function than those who had shunts later. The age at which the Fontan operation was performed did not seem to influence left ventricular function.

Quality of life

School and employment—Five of the 10 survivors had been so disabled in childhood that they had attended schools for the handicapped. Eight now work full time or are at college or school. One (case 7) had a problem with drugs and alcohol during adolescence but is now employed full time. Two patients cannot find employment; one of them (case 5) with a grade 3 ability index is awaiting further reoperation.

Marriage—Three patients (two men) have married; a woman (case 1) has no children, has had a nervous breakdown and is now divorced. The two men (cases 2 and 7) are married and have five normal children. Two unmarried women (cases 5 and 6) take the combined oral contraceptive pill without complication.

Driving and life insurance—All six patients who applied for driving licences have obtained them subject to review. Only one patient (case 2) has obtained

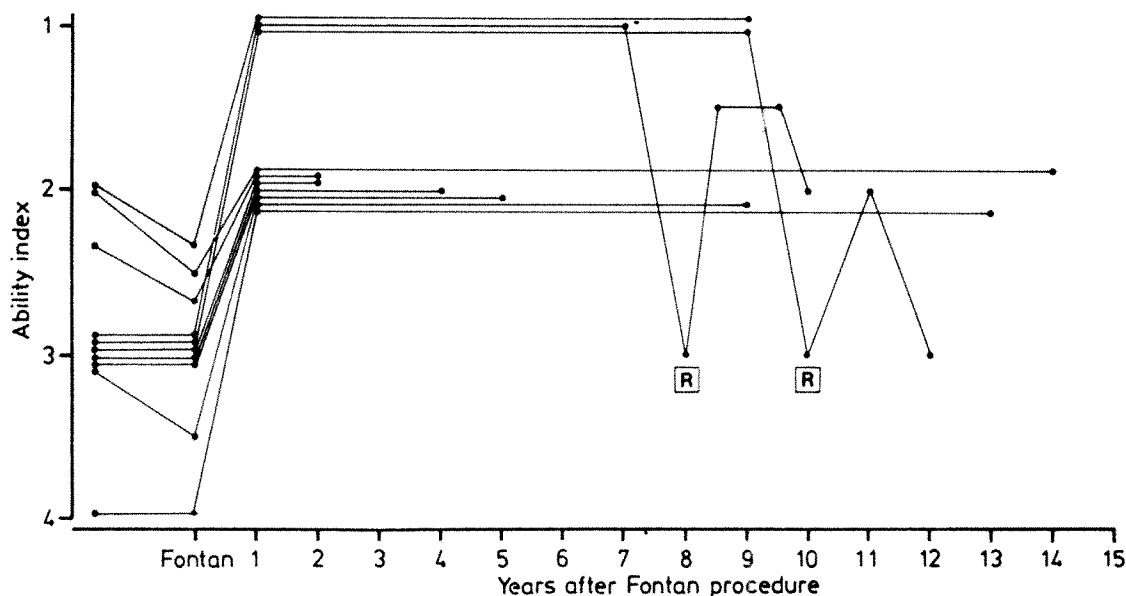


Fig 4 Change in ability index of 10 patients before and after the Fontan operation. R; reoperation.

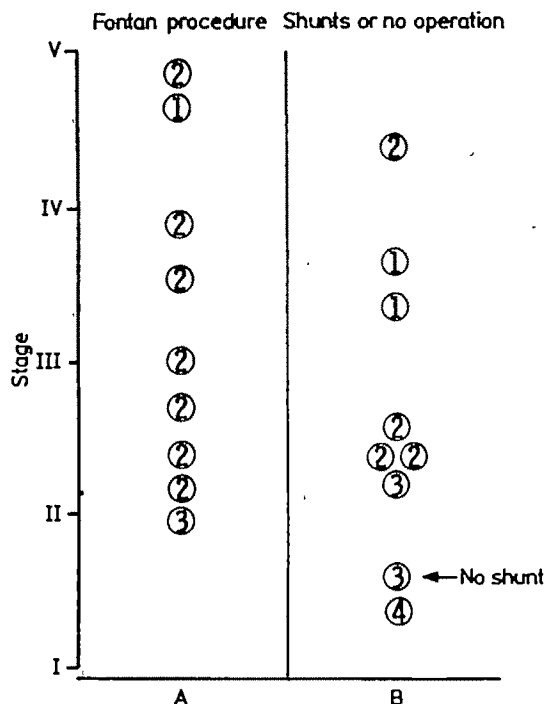


Fig 5 Exercise capacity according to the modified Bruce protocol of nine patients with a Fontan operation and nine patients with palliative shunts or no operation. Ability index of each patient is shown.

life insurance (with substantial loading); the others did not try for life insurance.

Medication—Three patients (cases 1, 3, and 7) take no medication; the seven others are taking diuretics or antiarrhythmic treatment or both. There are no extracardiac problems.

GROUP 2: PATIENTS WITH EXTRACARDIAC PALLIATIVE PROCEDURES OR NO PREVIOUS OPERATION

Fourteen patients aged 17–35 years (table 2) had either arteriopulmonary shunts (7) or a Glenn anastomosis (2), or both (4) and one (case 17) reached the age of 32 years without surgery but there had been a deterioration in ability index to 3 in the past three years. When she was 24 and the oxygen saturation was 81% and the pulmonary artery pressure was 18/15 mm Hg she was regarded as suitable for a Fontan operation. She refused operation until the age of 32 years when arterial oxygen saturation was 70%. At reinvestigation the pulmonary artery pressure could not be measured. At operation for an intended Fontan procedure the pulmonary artery pressure was 60 mm Hg. Because her hypoxic symp-

toms were related to the development of pulmonary vascular disease she was considered to be inoperable.

There are two survivors with only a functioning Glenn anastomosis performed at age 14 years (case 21) and two months (case 25). A patient (case 9, age 18) with a functioning Glenn anastomosis and Blalock Taussig shunt is well and does not wish to have further surgery at this time. One patient (case 21) is awaiting a Fontan operation and another (case 25), who attends another hospital, declines investigation.

Mortality

Four patients aged 17–30 years died; one (case 26) unexpectedly at the age of 30, eight years after an aortopulmonary Dacron shunt at 22 years. Patient 27, aged 19 years, with pulmonary atresia was seriously disabled for five years and died of pulmonary hypertension caused by his previous Blalock-Taussig shunt and of chronic left ventricular failure from aortic regurgitation. Patient 28 was severely hypoxic with syncope and thrombosed pulmonary arteries and he died aged 18 after a fourth attempt to establish a shunt. A girl (case 29) with two previous shunts died aged 17 years with left ventricular and renal failure caused by glomerulonephritis that required dialysis. She died after cardiac transplantation because the pulmonary artery pressure was raised and the right ventricle of the transplanted heart failed.

Arrhythmias

Six of the 10 patients have arrhythmias. These caused symptoms in two at ages 26 (case 18) and 30 years (case 17). When atrial fibrillation developed in patient 18, 24 years after a Potts operation, severe right sided congestion and ascites also developed, but she rapidly improved after cardioversion to sinus rhythm. Three years later she had complete heart block that caused syncope and required pacing. Atrial tachycardia in case 17 is controlled by verapamil.

Asymptomatic arrhythmias were found in four patients. One had non-sustained atrial tachycardia (case 23); another (case 16) had episodes of atrio-ventricular dissociation, sinus arrest, and junctional rhythm; and the other two patients had ventricular arrhythmias, either frequent ventricular extrasystoles (case 20) or couplets (case 24). Arrhythmias were not more frequent in those with reduced left ventricular ejection fraction.

Functional status of survivors

The 10 survivors aged 18–35 years (mean 25) have some cyanosis at rest, but ability indices show that seven lead nearly normal lives (table 2). Nine performed the symptom limited exercise test and were

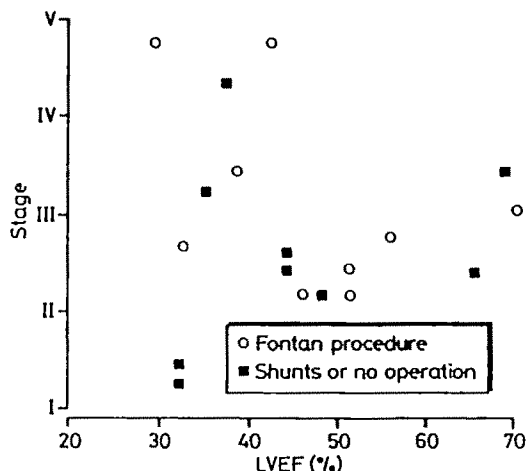


Fig 6 Exercise capacity and left ventricular ejection fraction (LVEF) of nine patients with a Fontan operation and nine patients with palliative shunts or no operation. There is no correlation between these two variables.

stopped by leg fatigue, dyspnoea, or both, with increasing cyanosis. Two patients were limited to stage I. None developed arrhythmias during exercise. Figure 5 shows the exercise capacity and ability index of each patient. There appeared to be no correlation between these two results.

Radionuclide measurement of left ventricular ejection fractions ranged from 32% to 69% (mean 46) (table 2). Those with longstanding or multiple shunts did not have worse left ventricular function than the others. In the two patients (cases 21 and 25) with a Glenn anastomosis the measured ejection fraction is 66% in one and is probably good in the other who refuses investigation. There was no correlation between left ventricular ejection fraction and exercise capacity (fig 6) or ability index (fig 7).

Quality of life

School and employment—Three patients attended schools for the handicapped. Six patients are now working. The other patients feel unable to work, except for patient 23 who has completed a youth training scheme and cannot find employment.

Marriage—Two patients (cases 16 and 18) married. Case 16 has two normal children. The woman (case 18) was sterilised and is now separated from her husband; the marriage broke up because her husband could not cope with her illness.

Driving and life insurance—Five patients have obtained driving licences, one (case 20) has an invalid car and one is a taxi driver. One patient (case 17) has obtained life insurance and another was turned down. No others tried for it.

Medication—Three patients take no medication and the others are on diuretics or antiarrhythmic treatment or both.

Extracardiac problems—Four patients have extracardiac problems. Case 18 has scoliosis. There was a cerebrovascular accident at the time of a further unsuccessful surgical shunt in case 19 and he has a detached retina and bilateral ankle arthropathy. Patient 25 has epilepsy related to a cerebrovascular incident during catheterisation in infancy. Patient 22 is a carrier of hepatitis and has chronic painful arthropathy.

Discussion

This group of patients has been selected by their achieving maturity. This and their referral from other centres because of problems may explain the high frequency of complications. Thus, these patients may not be truly representative of the incidence of complications in adolescence and adult life. This review, however, does show what can happen in late survivors with tricuspid atresia and normally related great arteries. Because this is the simplest

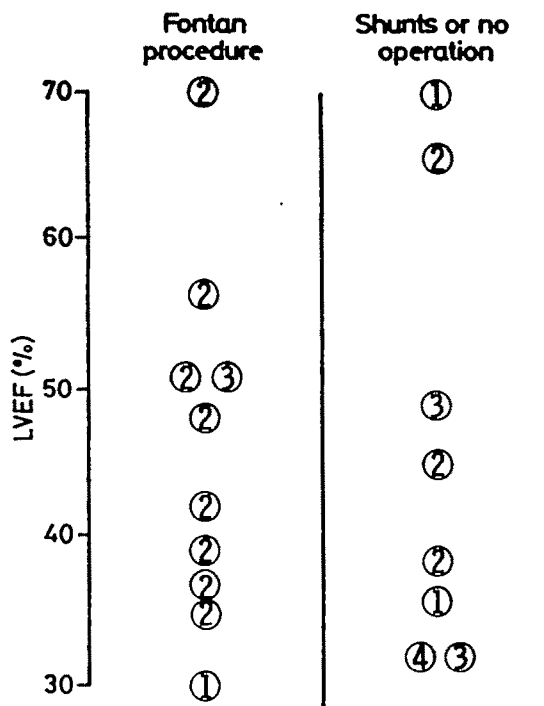


Fig 7 Left ventricular ejection fraction (LVEF) of 10 patients with a Fontan operation and eight with palliative shunts or no operation. The ability index of each patient is shown.

form of tricuspid atresia, it presumably is the type with the most favourable prognosis. Many patients had palliative procedures during the 1960s and early 1970s. Much has been learnt since then and techniques have been improved. Some of the complications we saw may not occur in the future.

The status of those who had a Fontan procedure (group 1) is slightly better than those who had palliative procedures (group 2). These marginal differences are reflected in better ability indices, greater exercise capacity, and fewer social and extracardiac problems. There is no difference, however, in left ventricular ejection fraction between the two groups, nor in the incidence of arrhythmias, which are common in both groups and probably age related.

Despite measured limitation of exercise capacity and left ventricular ejection fraction, many patients in both groups lead nearly normal lives as judged by the ability index. In both groups marriage and interpersonal relationships have been more successful for the men than for the women. All the offspring are normal. No women have had children in this series and it seems unlikely that any could have a successful pregnancy at the present time. The need for reoperation in both groups is similar but could have been reduced in the Fontan group by more meticulous surgical technique and the avoidance of Dacron conduits. Mortality in groups 1 and 2 was similar and often occurred when operative procedures were performed on patients with left ventricular dysfunction, pulmonary hypertension, or small pulmonary arteries.

The ability index gives a more useful assessment of the quality of life and the ability to lead it than the New York Heart Association classification, which is the conventional assessment of disability and really measures effort tolerance. The ability index is based on a positive rather than a negative approach and reflects a patient's ability to adapt to his physical problems. Thus it assesses the "distress" caused by illness as well as effort tolerance and these two factors are important when judging the normality and quality of life.

Radionuclide measurement of left ventricular ejection fraction in tricuspid atresia offers a non-invasive method of studying left ventricular function¹ but there may be difficulty in determining the left ventricular contour in the presence of a ventricular septal defect and a small outlet chamber. Thus we have some doubts about the accuracy of our measurements and do not reject a patient for a Fontan procedure on the basis of a single result by this technique alone. Few patients had left ventricular angiography within a reasonable time of the radionuclide study and so the results cannot be com-

pared; but left ventricular ejection fraction was also assessed in each patient by cross sectional echocardiography and these results were similar. Nuclear magnetic resonance studies of left ventricular function are more likely to be accurate and we are assessing their usefulness.

Although volume overload from previous shunts might be expected to impair left ventricular function, the effects are unpredictable and those patients with arteriopulmonary shunts inserted in infancy did not have worse left ventricular function than the others. Similarly, the age at which the Fontan operation was performed did not appear to influence left ventricular function in any way. Thus there is no straightforward relation between left ventricular function and duration of volume overload nor between left ventricular function and the degree of clinical hypoxia. Previous angiographic studies have also failed to find correlations between these variables.^{2,3} It seems likely that although volume overload is an important cause of left ventricular dysfunction, other factors must exert some influence. Notably, the one patient who did not have surgery (case 18) had an ejection fraction of only 32%. Since the left ventricle itself is intrinsically abnormal in this condition, the long term function is unpredictable. Subtle differences from normal left ventricular function have also been reported previously in patients with univentricular-atrioventricular connection and normal ejection fraction.⁴ In addition, some ventricular function appears to be lost at the time of Fontan operation and, perhaps because the ventricle is abnormal, left ventricular function appears to deteriorate with time. Coronary-bronchial collaterals may contribute to left ventricular deterioration by causing a steal phenomenon and these vessels were found in three patients in this series; in one they caused angina. This complication may well be a cause of late symptoms in adults with tricuspid or pulmonary atresia who have repeated thoracotomies, particularly mediastinal surgery.

Arrhythmias occurred in 50% of the survivors, and they were equally common in both groups. All patients except one were older than 20 years at the onset of the arrhythmia; thus it appears to be part of the natural development of the disease. Ambulatory electrocardiographic monitoring may detect arrhythmias in symptom free patients and we believe that it should be performed annually in all patients. The one patient (case 18) in whom complete heart block developed posed a difficult problem in siting the pacemaker wire. To avoid the complications of epicardial and left ventricular pacing, she was paced successfully from the coronary sinus and has remained well for a year.

It is important to decide which form of palliation

is most likely to lead to survival into adulthood. Most patients (23 of 29 (79%)) needed operation before the age of 10, and 14 (48%) required it during infancy. Because different surgeons performed different palliative procedures it is difficult to determine which was the most successful procedure. Similar dangers are inherent in both Potts and Waterston anastomoses because they tend to be too large, to damage a pulmonary artery, to increase pulmonary vascular resistance, or overload the left ventricle. Such anastomoses certainly caused problems in three patients when subsequent Fontan operations were undertaken (cases 11, 12 and 13). In one other patient with a Waterston anastomosis left ventricular failure was so severe that cardiac transplantation was all that could be considered. In some patients, however, these shunts provided satisfactory palliation, and three patients had successful Fontan procedures 4–15 years later. Two patients who had a Potts shunt at six and 18 months (cases 20 and 18) have adequate left ventricular function in sinus rhythm, but one has a stenosed shunt and the other has pulmonary hypertension. Because of problems such as these we do not recommend these shunts for early palliation.

It has been difficult to evaluate the role of the Glenn operation because only two of the 11 patients with a Glenn anastomosis survived with that as the sole palliation. Both retained good left ventricular function, as did the others with Glenn anastomoses, before they had further surgical interventions. A considerable number of patients suffer clinical deterioration within a decade of the Glenn anastomosis being created. This is the result of demands increased by growth and age or a decrease in pulmonary blood flow or both.⁵ In two patients in our series stenosis or occlusion of the anastomosis developed. Other major problems include the development of arteriovenous fistulas in the right lung, which have been demonstrated in three of our patients, caval collaterals, and fistulisation of the superior vena cava–right atrial junction,⁶ which occurred in two. Thus there may be long term problems with a Glenn anastomosis but the anastomosis is good for the long term function of the left ventricle, which is critical in this disease.

The best initial palliation appears to be the Blalock-Taussig shunt^{7,8} modified with Goretex interposition and carried out with impeccable technique to prevent distortion of the pulmonary arteries. The size of the shunt must be controlled so that the left ventricle is not overloaded. Eighteen (62%) of the 29 patients in this series had a Blalock-Taussig shunt performed. In one patient (case 27) with pulmonary atresia a Blalock-Taussig shunt caused pulmonary hypertension and he died sud-

denly. The others with this shunt have no serious long term complications. Two patients who survive with Blalock-Taussig shunts (cases 22 and 23) have measured impairment of left ventricular function but lead normal lives.

Whatever type of palliation is chosen, early post-operative investigation in the first year is mandatory to ensure that the pulmonary arteries are not distorted, that both pulmonary arteries are perfused, and that the shunt is not so large that it is predisposing the patient to premature left ventricular dysfunction or pulmonary vascular disease. So often these features are found too late when the patient is referred for further surgery after clinical deterioration. These patients must have careful regular non-invasive measurement of left ventricular function and of cardiac size, and determined efforts must be made to measure pulmonary artery pressure and calculate pulmonary vascular resistance. We recognise that calculation of pulmonary vascular resistance may be inaccurate because of the assumptions inherent in the method.

Natural long term survival, although infrequent, is possible in patients with tricuspid atresia and normally related great arteries, and survival to 51 years without surgery has been reported.⁹ Such survival requires a ventricular septal defect that is not so large in infancy that it causes irreversible failure or pulmonary hypertension and yet not so small as to cause profound hypoxia. The association of pulmonary valve stenosis with a large ventricular septal defect may also permit long term survival. When this occurs the right ventricular outflow tract is of good size, as are the pulmonary arteries, and such patients should be suitable for Fontan procedures or a modification. This was the case in only two of our four patients who reached 20 years without palliation (cases 1 and 26), but patient 26 had a palliative procedure before the Fontan procedure was devised.¹⁰ Two were not suitable for a Fontan procedure: one because of small pulmonary arteries (case 19) and the other because of pulmonary vascular disease (case 17).

The best management for patients with symptomatic tricuspid atresia in adolescence and adulthood has yet to be determined. The Fontan operation has a place in the management of older patients (≥ 14 years) but mortality is high—50% in this series. The high mortality is related to errors in selection. Results in survivors are good and are maintained provided that Dacron conduits are not used and that strict selection criteria are adhered to. Impeccable surgery is mandatory. Eight older patients had shunts which relieved hypoxic symptoms, provided that a Dacron interposition was not used and that the pulmonary arteries were not already throm-

bosed. A Waterston or Potts shunt at this age tended to produce progressive deterioration in left ventricular function, precluding a successful Fontan procedure. We feel the Fontan procedure is the better option if the ideal criteria are fulfilled. If not, then a Blalock-Taussig shunt is, once again, the shunt of choice. If left ventricular function is too poor cardiac transplantation is the only option. Those with palliative shunts will probably require both heart and lung transplantation because of pulmonary vascular disease and there will be difficulties with bleeding at the site of the previous thoracotomy. Whether patients in whom a Fontan procedure has been performed in childhood will do as well as those with palliative shunts remains to be determined.

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Effects of verapamil on haemodynamic function and myocardial metabolism in patients with hypertrophic cardiomyopathy

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SUMMARY The effect of 20 mg dose of intravenous verapamil was studied over a range of heart rates in 12 patients with hypertrophic cardiomyopathy. Six patients had an appreciable left ventricular outflow tract gradient and six did not. The drug reduced myocardial oxygen consumption in proportion to a reduction in the development of left ventricular pressure. The negative inotropic effect of verapamil was counteracted by the drug's non-specific vasodilator activity, so that cardiac index was unaltered at any heart rate and as a result myocardial efficiency was unaffected by the drug. Verapamil did not consistently alter myocardial metabolism. Some patients showed improvement in anaerobic myocardial metabolism after verapamil but an equal number showed impairment of lactate metabolism. It was not possible to predict from clinical features, echocardiographic findings, or haemodynamic variables measured before administration of verapamil which patients would demonstrate haemodynamic or metabolic improvement after the drug.

In this short term study no mechanism was demonstrated by which patients with hypertrophic cardiomyopathy might obtain a consistent improvement from treatment with verapamil.

Verapamil has been advocated for the treatment of patients with hypertrophic cardiomyopathy^{1 2} although the rationale for such treatment is unclear. The animal models of cardiomyopathy on which this treatment was proposed have no proven relation with human hypertrophic cardiomyopathy.² Furthermore, the early promise^{3 4} that verapamil treatment would reverse left ventricular hypertrophy in patients with hypertrophic cardiomyopathy is now disputed.⁵ Nevertheless, verapamil treatment is claimed to improve symptoms and exercise tolerance^{5 6} despite its failure consistently to improve systolic⁶ or diastolic left ventricular function⁷ and an absence of information about the metabolic effects of the drug in this disease.

We have investigated the metabolic and haemodynamic changes induced by verapamil over a range of heart rates to see whether we could find a

consistent beneficial action of the drug. We also compared the response to the drug in a group of patients who had left ventricular outflow tract gradients with the response in a group who did not, to determine whether any beneficial effect of the drug is dependent on the presence of an outflow gradient.

Patients and methods

We studied 12 symptomatic patients with the physical signs and echocardiographic features of hypertrophic cardiomyopathy. They were all normotensive and none had valvar heart disease or coronary artery disease.

Two groups of six were defined during preliminary diagnostic cardiac catheterisation. Group A, the non-obstructed group, consisted of four patients in whom no left ventricular intracavity gradient was present at rest, on post-extrasystolic beats, or during amyl nitrite administration and two patients in whom a gradient of < 20 mm Hg could be provoked. Group B, those with obstruction consisted of four patients with a resting left ventricular

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Table 1 Clinical details and echocardiographic features of the patients with hypertrophic cardiomyopathy

Clinical details	Group A (non-obstructed)	Group B (obstructed)
Male	3	2
Female	3	4
Age (years):		
Range	17-57	40-63
Mean	37	51
Symptoms:		
Chest pain	5	5
Dyspnoea	5	5
Syncope/palpitation	1	—
Family history of hypertrophic cardiomyopathy:		
Definite	3	—
Probable	1	4
Echocardiographic dimensions (mean (SEM)) (mm):		
Left ventricular end diastolic diameter	47.3 (2.0)	41.8 (3.3)
Left ventricular end systolic diameter	29.8 (2.5)	23.8 (2.8)
Interventricular septal thickness	20.5 (2.4)	21.3 (1.4)
Left ventricular posterior wall thickness	10.8 (0.7)	12.0 (1.5)

intracavity gradient of >35 mm Hg (maximum 164 mm Hg) and two patients with resting gradients of <20 mm Hg which rose to greater than 50 mm Hg after amyl nitrite. Data from the two groups were analysed separately and in combination. Table 1 gives the clinical details of patients.

Each patient gave informed written consent to the study which had the approval of the hospital ethics committee. Before the study four patients receiving propranolol and two who were taking verapamil had these drugs stopped for at least 48 hours. Diuretics were continued in the four group A and three group B patients receiving them. One patient with obstruction (group B) received carbimazole and another took thyroxine. These drugs were continued and the patients were euthyroid at the time of the investigation.

The study was performed after an overnight fast. Diazepam 10 mg and atropine 0.6 mg were given intramuscularly as premedication one hour before cardiac catheterisation. At the same time intravenous heparin (45 units/kg) was given to minimise the effect of a subsequent dose of heparin on free fatty acid concentrations.⁸ Routine cardiac pressures were measured and coronary arteriography was performed via catheters inserted under local anaesthesia with lignocaine. A second dose of heparin was given immediately after arterial catheterisation. The left ventricular outflow gradient was measured by catheters positioned in the left ventricular body transseptally via the interatrial septum and retrogradely across the aortic valve. An intracavity gradient was provoked as described above.

After we confirmed consent to proceed with the research study, we positioned a number 8 French gauge catheter with a micromanometer tip (Gaeltec or Millar) transseptally in the left ventricular body by means of the long sheath technique. It was used to record high fidelity pressure and for left ventricu-

lar cineangiography (with 76% Urografin). Aortic pressure was measured with a fluid filled catheter, cardiac output by dye dilution, and coronary sinus flow by thermodilution.

Pressures were measured with reference to the sternal angle. Pressure, micromanometer, and thermistor signals were displayed on a Cambridge 12 channel recorder, stored on magnetic tape, and processed by on line computer. Contractility indices including the maximum rate of rise of left ventricular pressure (dP/dt_{max}), dP/dt_{max} divided by developed pressure ($dP/dt_{max} \div P$), and the product of the series elastic stiffness constant and the velocity of contractile shortening at zero load (KV_{max}) were derived from the micromanometer signal.

More than 30 minutes elapsed between arteriography and subsequent measurements. Pressures and flows were measured and arterial and coronary sinus blood were sampled simultaneously for measurement of metabolite contents at the basal heart rate (sinus rhythm) and during coronary sinus pacing. Subjects were paced where possible at 25, 50, and 75 beats/minute above their pre-verapamil basal rate ($+25$, $+50$, $+75$). Left ventricular cineangiography (right anterior oblique projection) was then performed during pacing at 10 beats/minute above the basal heart rate. Twenty minutes later 20 mg of verapamil was infused intravenously over two minutes. Seven minutes after the verapamil infusion haemodynamic measurements and metabolite sampling were repeated at the intrinsic heart rate and then, where possible, during pacing at identical heart rates to those used earlier. A second left ventricular cineangiogram was performed at a paced rate identical to that used for the first angiogram. Post-verapamil measurements and angiography were completed within 40 minutes of drug administration in each case.

The oxygen content and concentrations of lactate,

pyruvate, hydroxybutyrate, acetoacetate, glycerol, and free fatty acid in arterial and coronary sinus blood were determined.⁸ Derived haemodynamic and metabolic variables were calculated by standard formulas. Left ventricular volumes (Dodge method) were calculated by planimetry.

We used the paired *t* test, the *t* test for small samples, and linear regression as appropriate for statistical analysis. Values are expressed as mean (1 SEM). A value of $p < 0.05$ was regarded as statistically significant.

Results

HAEMODYNAMIC EFFECTS OF VERAPAMIL

In the basal state all patients were in sinus rhythm (rate 74.6 (4.8) beats/minute). Five patients could be paced to +75, another five to +50, and two patients could be paced only to +25.

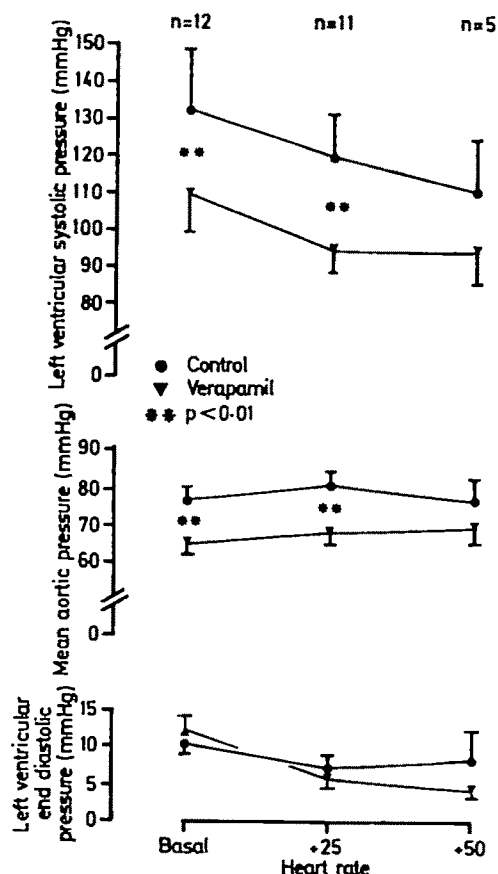


Fig 1 Effect of verapamil on left heart pressures (mean (SEM)) in hypertrophic cardiomyopathy.

After intravenous verapamil complete heart block developed in one patient and one had a nodal bradycardia. Both arrhythmias resolved spontaneously within the seven minute period allowed before measurements were made. The post-verapamil basal rate (70.2 (3.6) beats/minute) was not significantly different from the pre-verapamil basal rate. After verapamil only two patients could be paced to +75 and another three to +50. One patient could not be paced at all after verapamil. The highest average paced rate pre-verapamil was 131.5 (4.6) beats/minute and post-verapamil it was 111.2 (6.5) beats/minute ($p < 0.01$).

Figures 1-6 show the haemodynamic effects of verapamil at the heart rates chosen. Only patients who could be paced at the specified heart rates pre-verapamil and post-verapamil are included in the analysis. Data from the two patients who could be paced to +75 both before and after verapamil are

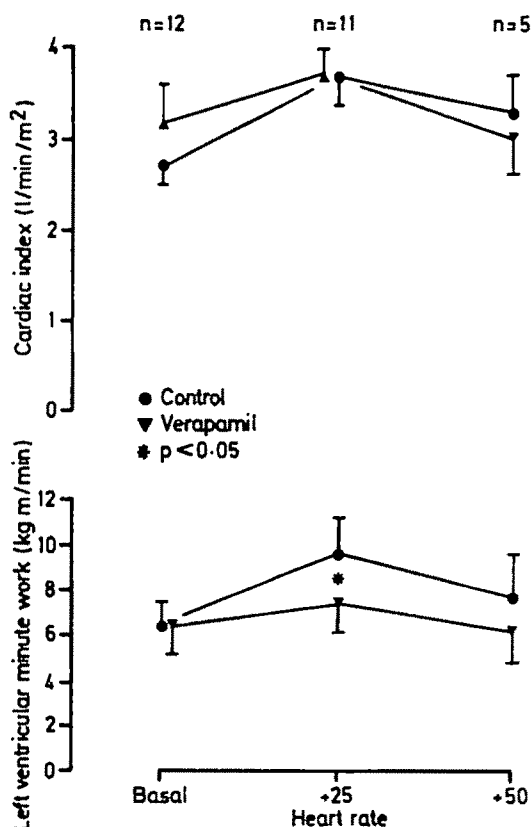


Fig 2 Effect of verapamil on cardiac index and left ventricular minute work (mean (SEM)) in hypertrophic cardiomyopathy.

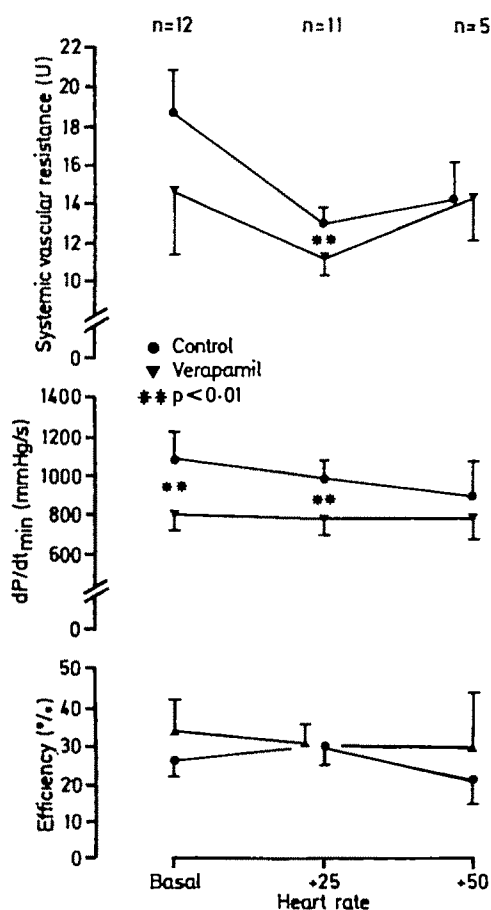


Fig 3 Effect of verapamil on systemic vascular resistance, dP/dt_{min} and efficiency (mean (SEM)) in hypertrophic cardiomyopathy.

not suitable for statistical analysis. These data, however, resembled the effects in the larger group at +50.

Verapamil did not significantly alter the peak left ventricular outflow tract gradient at any heart rate in the group of 12 patients or in the subgroup with obstruction (group B), although the gradient tended to fall at each heart rate after verapamil. In group B the basal gradient was 61.7 (27.5) mm Hg and after verapamil the gradient was 47.2 (17.7) mm Hg.

Verapamil did not alter the cardiac index significantly at any heart rate (fig 2), so that the small reduction in left ventricular minute work after verapamil at +25 ($p < 0.05$) is the result of reduced pressure development.

The reduction in total systemic vascular resistance was statistically significant with pacing at +25 but just failed to achieve significance at the

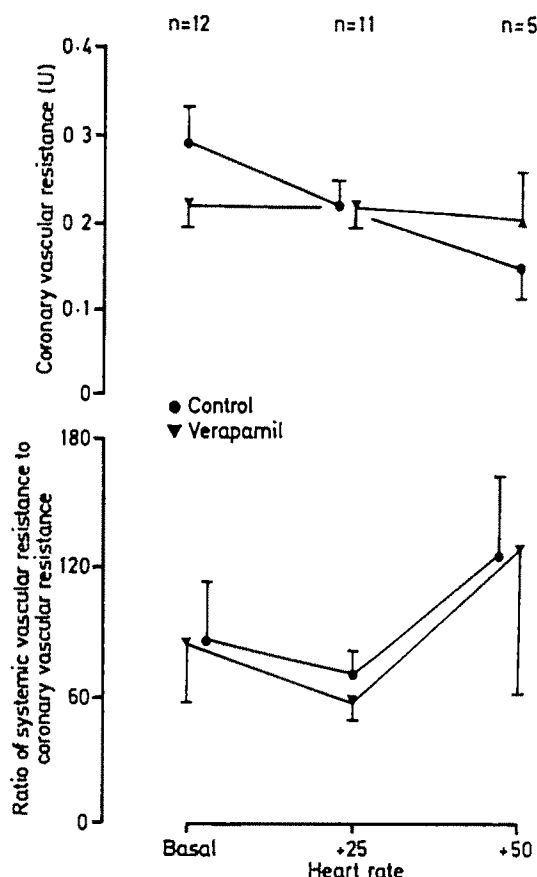


Fig 4 Effect of verapamil on coronary vascular resistance and the ratio of systemic vascular resistance to coronary vascular resistance (mean (SEM)) in hypertrophic cardiomyopathy.

basal rate ($0.05 < p < 0.1$) (fig 3). The reduction in coronary vascular resistance after verapamil also just failed to achieve significance at the basal rate ($0.05 < p < 0.1$) (fig 4). Verapamil did not affect systemic or coronary vascular resistances at higher rates. It was notable that with increasing heart rates coronary vascular resistance fell progressively in 11 of the 12 patients before verapamil but after the drug it was not altered by pacing.

In one patient pacing could not be re-established after verapamil and no second left ventricular cine-angiogram was performed. Figure 7 shows the angiographically derived data for the remaining eleven patients.

METABOLIC EFFECTS OF VERAPAMIL

Myocardial extractions, extraction ratios, and oxygen extraction ratios of lactate (table 2) and, to a

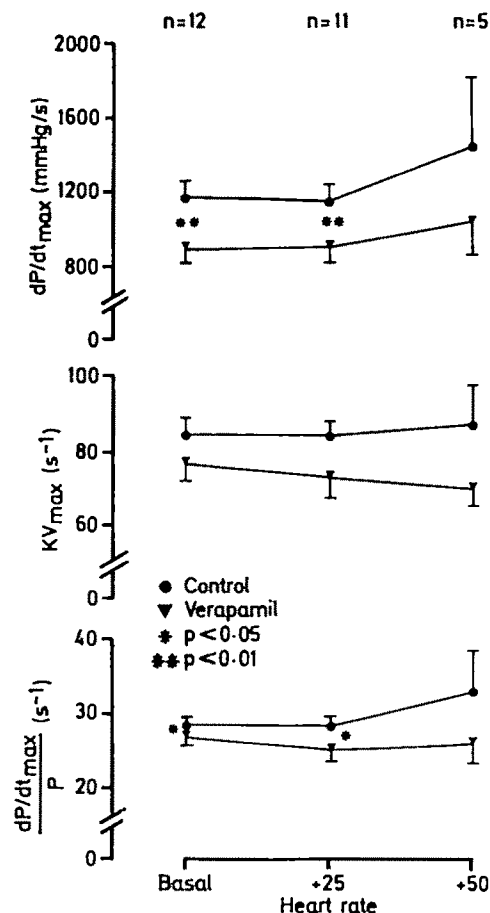


Fig 5 Effect of verapamil on indices of contractility in hypertrophic cardiomyopathy (mean (SEM)).

lesser extent, pyruvate (table 3) were reduced at higher heart rates. Verapamil did not affect the overall myocardial metabolism of these substrates in the group of patients studied although it had clinically important effects in some individuals.

In two patients with abnormal lactate extraction (0–10%) pre-verapamil, normal lactate extraction developed at identical heart rates after the drug. A further patient who had been a lactate producer (–16%) at high heart rates pre-verapamil could not be paced rapidly after the drug and thus had normal lactate extraction (41%) at the highest rate achieved after the drug. Three patients had normal lactate extraction pre-verapamil that became impaired after the drug. One developed abnormal lactate extraction at an identical heart rate after verapamil and two became lactate producers at lower rates.

In the remaining six patients verapamil had no major effect on lactate metabolism. Five patients had

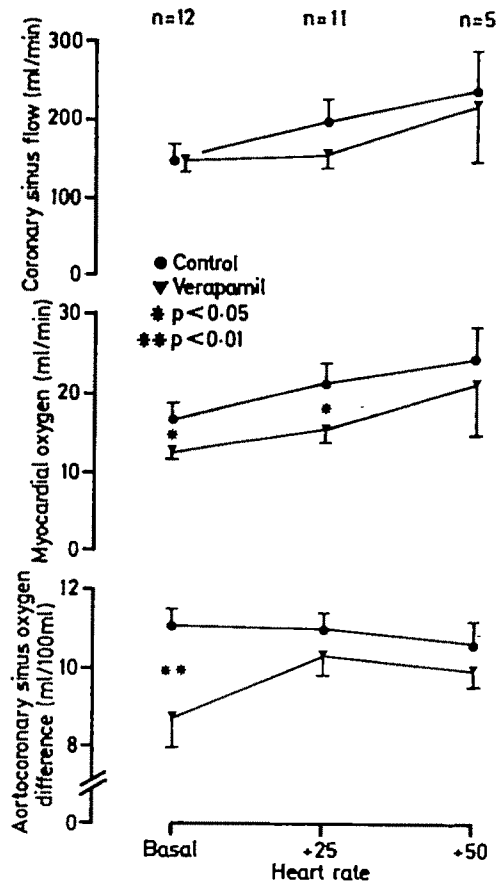


Fig 6 Effect of verapamil on myocardial metabolism in hypertrophic cardiomyopathy (mean (SEM)).

normal myocardial lactate extraction (>10%) at all heart rates before and after verapamil but after verapamil the highest average heart rate achieved by these patients was 35 beats/minute below that achieved before verapamil. A further patient produced myocardial lactate at comparable heart rates before and after verapamil.

After verapamil the arterial concentration of ketone bodies (tables 4 and 5) tended to rise whereas coronary sinus concentrations were less affected. As a result extractions, extraction ratios, and oxygen extraction ratios of ketone bodies tended to increase after verapamil. The changes did not always achieve statistical significance and were more apparent for acetoacetate than hydroxybutyrate. (Blood samples for hydroxybutyrate estimation from one patient were accidentally destroyed.) The myocardial metabolism of glycerol (table 6) and free fatty acid (table 7) were not affected in any consistent way by verapamil.

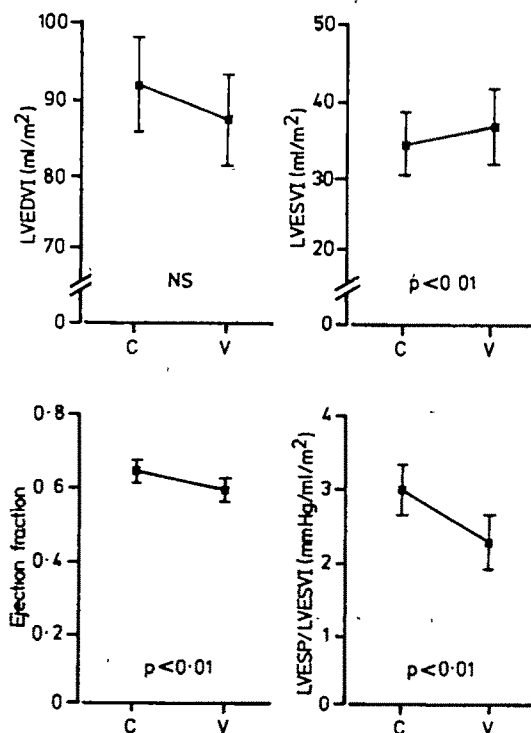


Fig 7 Haemodynamic effects (mean (SEM)) of verapamil in eleven patients with hypertrophic cardiomyopathy at constant paced heart rate. C, control; V, verapamil; LVEDVI, left ventricular end diastolic volume index; LVESVI, left ventricular end systolic volume index.

There was no clear relation between control haemodynamic variables and changes in myocardial metabolism after verapamil—no subgroup showing a metabolic improvement after the drug could be identified from control values for haemodynamic variables. The alteration in myocardial oxygen con-

sumption after verapamil was, however, directly related to the change in left ventricular systolic pressure (fig 8) but was not related to changes in left ventricular filling pressure, cardiac index, systemic vascular resistance, or contractility indices. In group B there was a suggestion that changes in myocardial oxygen consumption were directly related to alterations in outflow gradient ($0.05 < p < 0.1$).

COMPARISON OF GROUPS A AND B

By definition the left ventricular outflow gradient was higher in group B patients (with obstruction) than in group A. This was true at all heart rates, both before and after verapamil. Consequently the left ventricular peak systolic pressure was higher in group B than in group A, so that aortic pressures in the two groups did not differ. After verapamil, mean aortic pressure tended to fall less in group A than in group B at each heart rate (at basal heart rate, 9.8 (3.0) vs 15.2 (3.8) mm Hg; at +25, 7.3 (2.2) vs 20.8 (5.0) mm Hg); however, these differences were only significant with pacing at +25.

Although basal heart rates were similar in the two groups, it was possible to pace group A to higher rates than group B after verapamil. Thus four patients in group A but only one in group B could be paced to +50 and only group A patients could be paced to +75 after verapamil.

Normalised left ventricular end diastolic volume was significantly greater in group A than in group B both before (104.8 (5.9) vs 77.2 (8.0) ml/m²) and after verapamil (99.6 (7.6) vs 73.2 (3.9) ml/m²) but left ventricular end systolic volume indices and ejection fractions were not significantly different. At comparable heart rates in the control state myocardial oxygen consumption tended to be higher in group A than in group B although not significantly so. Myocardial oxygen consumption fell after verapamil in each group but the change was greater in group B. Thus after verapamil the differences in

Table 2 Lactate metabolism in patients with hypertrophic cardiomyopathy (mean (SEM))

	Basal (n = 12)	Basal + 25 (n = 11)	Basal + 50 (n = 5)
Arterial concentration (mmol/l):			
Control	0.573 (0.080)	0.654 (0.090)	0.506 (0.042)
Verapamil	0.628 (0.113)	0.675 (0.142)	0.495 (0.035)
Coronary sinus concentration (mmol/l):			
Control	0.385 (0.050)	0.406 (0.053)	0.447 (0.060)
Verapamil	0.428 (0.060)	0.459 (0.067)	0.412 (0.055)
Extraction (mmol/l):			
Control	0.188 (0.048)	0.248 (0.052)	0.059 (0.032)
Verapamil	0.200 (0.067)	0.215 (0.086)	0.083 (0.045)
Extraction ratio (%):			
Control	28.9 (4.9)	36.6 (4.3)	12.8 (6.7)
Verapamil	28.6 (5.7)	26.7 (5.3)	16.5 (8.9)
Oxygen extraction ratio (%):			
Control	12.8 (3.3)	16.4 (3.0)	3.9 (1.9)
Verapamil	16.4 (4.2)	14.3 (4.6)	6.8 (3.2)

Table 3 *Pyruvate metabolism in patients with hypertrophic cardiomyopathy (mean (SEM))*

	Basal (n = 12)	Basal + 25 (n = 11)	Basal + 50 (n = 5)
Arterial concentration (mmol/l):			
Control	0.060 (0.010)	0.060 (0.012)	0.048 (0.004)
Verapamil	0.060 (0.013)	0.063 (0.014)	0.053 (0.005)
Coronary sinus concentration (mmol/l):			
Control	0.039 (0.004)	0.037 (0.004)	0.039 (0.005)
Verapamil	0.038 (0.006)	0.040 (0.004)	0.043 (0.005)
Extraction (mmol/l):			
Control	0.021 (0.009)	0.023 (0.009)	0.008 (0.004)
Verapamil	0.021 (0.010)	0.024 (0.011)	0.010 (0.005)
Extraction ratio (%):			
Control	23.6 (10.4)	27.7 (10.0)	17.5 (8.0)
Verapamil	23.9 (11.2)	24.9 (9.1)	18.2 (8.3)
Oxygen extraction ratio (%):			
Control	1.3 (0.5)	1.3 (0.4)	0.6 (0.2)
Verapamil	1.7 (0.6)	1.3 (0.5)	0.7 (0.3)

Table 4 *Hydroxybutyrate metabolism in patients with hypertrophic cardiomyopathy (mean (SEM))*

	Basal (n = 11*)	Basal + 25 (n = 10*)	Basal + 50 (n = 4*)
Arterial concentration (mmol/l):			
Control	0.201 (0.064)	0.165 (0.062)	0.192 (0.109)
Verapamil	0.231 (0.065)	0.240 (0.057)	0.262 (0.078)
Coronary sinus concentration (mmol/l):			
Control	0.122 (0.041)	0.105 (0.039)	0.144 (0.070)
Verapamil	0.141 (0.038)	0.136 (0.034)	0.197 (0.058)
Extraction (mmol/l):			
Control	0.079 (0.023)	0.060 (0.022)	0.049 (0.040)
Verapamil	0.090 (0.029)	0.104 (0.025)	0.065 (0.025)
Extraction ratio (%)			
Control	43.0 (5.0)	36.6 (1.9)	16.9 (5.7)
Verapamil	34.4 (5.0)	44.7 (3.8)	25.0 (3.8)
Oxygen extraction ratio (%)			
Control	8.0 (2.4)	6.4 (2.5)	5.7 (4.7)
Verapamil	11.6 (3.7)	11.4 (2.7)	7.3 (2.6)

*The blood samples from one patient for estimation of hydroxybutyrate concentrations were accidentally destroyed.

Table 5 *Acetoacetate metabolism in patients with hypertrophic cardiomyopathy (mean (SEM))*

	Basal (n = 12)	Basal + 25 (n = 11)	Basal + 50 (n = 5)
Arterial concentration (mmol/l):			
Control	0.109 (0.023)	0.095 (0.024)	0.097 (0.034)
Verapamil	0.127 (0.028)*	0.132 (0.029)	0.139 (0.036)
Coronary sinus concentration (mmol/l):			
Control	0.066 (0.016)	0.056 (0.011)	0.059 (0.017)
Verapamil	0.068 (0.012)	0.067 (0.014)	0.080 (0.022)
Extraction (mmol/l):			
Control	0.043 (0.012)	0.039 (0.014)	0.038 (0.017)
Verapamil	0.059 (0.017)	0.165 (0.015)*	0.060 (0.017)
Extraction ratio (%)			
Control	33.8 (6.4)	34.1 (5.6)	35.4 (4.9)
Verapamil	35.8 (8.4)	48.3 (1.7)*	41.6 (6.3)
Oxygen extraction ratio (%)			
Control	3.9 (1.2)	3.8 (1.4)	3.8 (1.9)
Verapamil	7.3 (2.0)*	6.5 (1.5)*	6.2 (1.7)

*p < 0.05.

Table 6 Glycerol metabolism in patients with hypertrophic cardiomyopathy (mean (SEM))

	Basal (n = 12)	Basal + 25 (n = 11)	Basal + 50 (n = 5)
Arterial concentration (mmol/l)			
Control	0.073 (0.017)	0.058 (0.011)	0.053 (0.017)
Verapamil	0.074 (0.014)	0.079 (0.015)	0.054 (0.011)
Coronary sinus concentration (mmol/l)			
Control	0.065 (0.017)	0.045 (0.008)	0.043 (0.013)
Verapamil	0.066 (0.012)	0.069 (0.012)	0.045 (0.010)
Extraction (mmol/l)			
Control	0.009 (0.005)	0.013 (0.005)	0.010 (0.009)
Verapamil	0.008 (0.006)	0.010 (0.010)	0.009 (0.013)
Extraction ratio (%):			
Control	14.0 (8.2)	18.4 (9.2)	9.7 (12.3)
Verapamil	1.2 (13.1)	8.3 (8.6)	4.1 (19.9)
Oxygen extraction ratio (%):			
Control	1.0 (0.4)	1.2 (0.4)	1.0 (0.8)
Verapamil	1.5 (0.6)	1.3 (0.6)	1.2 (1.0)

Table 7 Free fatty acid metabolism in patients with hypertrophic cardiomyopathy (mean (SEM))

	Basal (n = 12)	Basal + 25 (n = 11)	Basal + 50 (n = 5)
Arterial concentration (mmol/l)			
Control	0.64 (0.07)	0.63 (0.09)	0.55 (0.09)
Verapamil	0.67 (0.07)	0.76 (0.08)	0.63 (0.13)
Coronary sinus concentration (mmol/l):			
Control	0.53 (0.08)	0.49 (0.08)	0.49 (0.05)
Verapamil	0.56 (0.08)	0.66 (0.07)	0.54 (0.11)
Extraction (mmol/l):			
Control	0.11 (0.02)	0.14 (0.03)	0.06 (0.04)
Verapamil	0.10 (0.03)	0.10 (0.05)	0.09 (0.03)
Extraction ratio (%):			
Control	19.6 (4.7)	21.8 (4.9)	8.6 (4.4)
Verapamil	17.6 (4.4)	13.5 (5.2)	12.8 (3.6)*
Oxygen extraction ratio (%):			
Control	58.1 (12.4)	74.5 (17.3)	34.3 (20.1)
Verapamil	77.4 (14.7)	63.0 (21.0)	50.8 (18.6)

*p < 0.05.

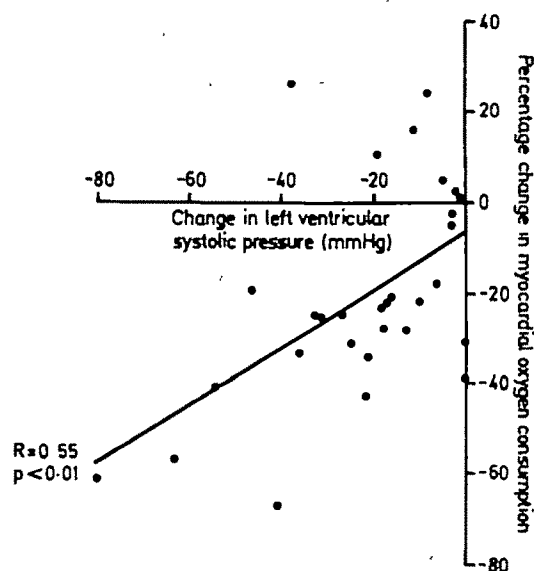


Fig 8 Relation between changes in left ventricular systolic pressure and myocardial oxygen consumption.

myocardial oxygen consumption between the groups became statistically significant (at basal rate, A 14.1 (1.0) vs B 10.9 (1.0) ml/min; at +25, A 18.9 (1.1) vs B 11.6 (1.2) ml/min; $p < 0.05$).

Verapamil produced no apparent difference in myocardial metabolism, as judged from metabolite concentrations, extractions, or extraction ratios, in the two subgroups at basal heart rate. When paced at +25 some differences were seen between the subgroups. Compared with the pre-verapamil state each patient in group B showed a reduction in lactate extraction (0.081 (0.030) vs 0.236 (0.068) mmol/l, $p < 0.05$), extraction ratio (19.3 (7.3) vs 37.7 (7.9)%, $p < 0.02$), and oxygen extraction ratio (5.9 (1.9) vs 15.6 (4.4)%, $p < 0.05$) but these were unchanged in the patients in group A.

We found no other haemodynamic or metabolic differences between the groups.

Discussion

We evaluated the effects of verapamil independently of the drug's heart rate effect by using fixed pacing rates. By studying the effect of the drug over a range

of heart rates it was possible to seek consistent changes in individual patients and the groups. Pacing also enabled us to apply stress and thus alter myocardial work and oxygen consumption, which are thought to be important determinants of symptoms and prognosis in hypertrophic cardiomyopathy.

The effects of intravenous verapamil on simple basal resting haemodynamics (heart rate, cardiac index, and left ventricular and aortic pressures) in this study accorded well with previous studies.^{2,6,9} In addition, the present study suggests that these effects of intravenous verapamil on cardiac index and pressures also apply at higher heart rates. It also confirms that although intravenous verapamil has little effect on left ventricular end diastolic volume,^{2,10} left ventricular end systolic volume increases and ejection fraction decreases.¹⁰

As in a previous study¹⁰ we observed a reduction in the left ventricular end systolic pressure to volume ratio, suggesting a reduction in left ventricular contractility because heart rate remained constant. These observations accord with our measurements of isovolumic contractile indices which indicate that verapamil has negative inotropic properties at all rates.

This reduction in left ventricular contractility explains the observations that outflow gradient usually fell despite afterload reduction. It would also explain the absence of a reduction in left ventricular end diastolic pressure and volume despite verapamil induced systemic vasodilatation.

Our observations that left ventricular end diastolic pressure and volume were unaltered by verapamil are counter to the finding by other groups of improved diastolic function in some but not all patients after acute intravenous verapamil¹⁰ and during long term oral drug treatment.⁶ The suggestion that verapamil may improve diastolic function is central to the argument by these groups that verapamil is a valuable drug for treating hypertrophic cardiomyopathy. Our contradictory findings could partly be accounted for by our measuring volume during coronary sinus pacing, with a consequent alteration of the timing of the atrial contribution to ventricular filling. Other data, however, suggest that any beneficial action of verapamil on ventricular filling is independent of this atrial contribution,¹¹ so that the protocol used should not have masked a beneficial action of verapamil on filling; we have previously failed to demonstrate a beneficial effect of the drug on ventricular isovolumic relaxation in this disease.⁷

At all rates the ratio of coronary to systemic vascular resistance was unaltered by verapamil. This suggests a non-specific vasodilating effect without a

specific coronary dilating action. Myocardial oxygen consumption was reduced by verapamil at all heart rates. The reduction was proportional to the reduction in left ventricular pressure development. Since cardiac index did not change, the efficiency of the left ventricle in performing external work was unaltered at any pacing rate.

For the whole group of patients intravenous verapamil produced no consistent improvement in myocardial metabolism. Similar numbers of patients showed adverse metabolic changes and metabolic improvement. Although verapamil reduced external work, myocardial ischaemia occurred at relatively low heart rates in some individuals as a result of reduced coronary perfusion pressure.

Clinical or echocardiographic features and data obtained at cardiac catheterisation before administration of verapamil could not be used to predict patients in whom myocardial metabolism would improve after the drug. There was no evidence that intravenous verapamil had effects on haemodynamic function and metabolism that differed in any clinically important manner in groups A and B.

This study suggests that the negative inotropic effects of verapamil may produce beneficial effects by reducing unproductive contraction. Such effects will lower myocardial oxygen consumption, wall tension, and the outflow gradient; however, the importance of the outflow gradient in producing symptoms is disputed.¹² At the same time reduced contractility will result in detrimental reductions of ejection pressure and flow and a higher filling pressure. The low flow and high filling pressures may be offset by the drug's systemic vasodilating properties, which will tend to reduce myocardial oxygen requirements further. Unfortunately, systemic vasodilatation will further reduce coronary perfusion pressure.

The only additional factor influencing myocardial energetics will be the effect of the drug on the coronary vessels. In all states coronary vascular resistance was low, which suggests that coronary vessels in patients with hypertrophic cardiomyopathy are almost maximally dilated. There is little reserve capacity for dilatation in response to increased work and the capacity of verapamil to dilate coronary vessels in these patients is therefore limited.

Whether the negative inotropic effect or systemic vasodilator effects predominate, intravenous verapamil can only lower myocardial oxygen consumption at the expense of reduced pressure development. Since verapamil has little effect on coronary vascular resistance, the only possibility of a myocardial mechanical advantage is when the reduction of myocardial oxygen consumption exceeds the

reduction in coronary flow resulting from reduced perfusion pressure. Generally such advantage was not detectable.

Our failure to demonstrate any major or consistent improvement in haemodynamic function or myocardial metabolism after administration of intravenous verapamil may be an important consideration when deciding whether patients should receive long term oral verapamil treatment. Certainly, our findings do not demonstrate a basis on which benefits from such treatment might arise.

It is therefore important to consider carefully those reports in which verapamil is claimed to improve symptoms and exercise tolerance. There have been several open studies in which patients, who had generally been selected because they had not responded favourably to β blockade, were found to have improved symptoms and exercise tolerance after verapamil.^{1 5 6} There has been only one randomised, double blind, placebo controlled trial of oral verapamil.¹³ The patients in this trial cannot be said to be unselected. Each patient had unacceptable symptoms or adverse effects during treatment with propranolol. Thirteen of the 19 patients in the trial had previously taken part in a short term study of the effects of intravenous verapamil,¹⁴ and presumably had demonstrated some benefit during this intervention. Despite the bias in patient selection, during a double blind comparison of placebo, propranolol, and verapamil, exercise performance during the verapamil phase was no better than during the propranolol phase and symptoms were improved almost as much by placebo as by verapamil. The treatment periods were short, however, and no adequately controlled long term trials of verapamil have been undertaken.

Thus the benefits of treatment of hypertrophic cardiomyopathy with verapamil are unproven and the evidence from this study suggests that any advantage is not clinically significant. Any potential benefits must be weighed against the danger of serious bradycardia, pulmonary oedema, and hypotension.⁵

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Left atrial myxoma: new perspectives in the diagnosis of murmur free cases

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SUMMARY No cardiological signs or symptoms were seen in three patients with left atrial myxomas. The diagnosis was established by cross sectional echocardiography. In two patients this investigation was performed to exclude a cardiac source of systemic emboli. The third patient had constitutional signs only. All three had raised erythrocyte sedimentation rates and C reactive protein concentrations. In two patients the myxomas were successfully excised; the third patient who had presented with massive peripheral and central embolisation died during emergency operation.

Cross sectional echocardiography is the technique of choice for detecting atrial myxomas and the absence of the cardiological signs should not preclude referral for diagnostic echocardiography.

Left atrial myxoma is the most common primary cardiac tumour and is one of the few for which operation offers a complete cure. Clinical findings are variable and non-specific and may mimic almost any other cardiovascular disorder.¹⁻⁵ Before echocardiography became available, diagnosis of left atrial myxoma, if suspected, was made by angiography or at necropsy or was an unexpected finding during cardiac operation. Cross sectional echocardiography has increased the number of myxomas that are diagnosed before operation.⁶⁻⁸

We report the clinical presentation, diagnosis, and management of three patients with left atrial myxoma seen over the past 12 months. These patients are representative of a wide spectrum of manifestations, the true cause of which may be missed when the myxoma does not produce a murmur.

Patients and methods

CASE 1

A 48 year old man with chronic aortic regurgitation

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was first seen at the Hammersmith Hospital at the age of 39 when he complained of lethargy and general malaise. M mode echocardiography and cardiac catheterisation suggested that the aortic regurgitation was only moderate and that aortic valve replacement could safely be deferred. An erythrocyte sedimentation rate of 50 mm in the first hour was also noted but a bacteriological search for endocarditis was negative.

Over the next six years the patient had continued constitutional symptoms and further enlargement of the heart was noted. At age 44 years his aortic valve was replaced with a Starr-Edwards prosthetic valve.

Surgical findings were consistent with the diagnosis. The aortic root was dilated and prevented competent apposition of the otherwise normal valve cusps. Although the postoperative period was uneventful, the patient continued to complain of lethargy and fatigue. There was no weight loss and numerous blood cultures and serological tests were all negative. Serum protein electrophoresis and quantitative immunoelectrophoresis showed a moderate increase in the α_1 and γ region which was polyclonal with no paraprotein. The concentration of C reactive protein was raised (48 mg/l; normal range for this laboratory <15 mg/l). The complement profile was normal and there were no heart muscle antibodies or rheumatoid factor. Six months later at

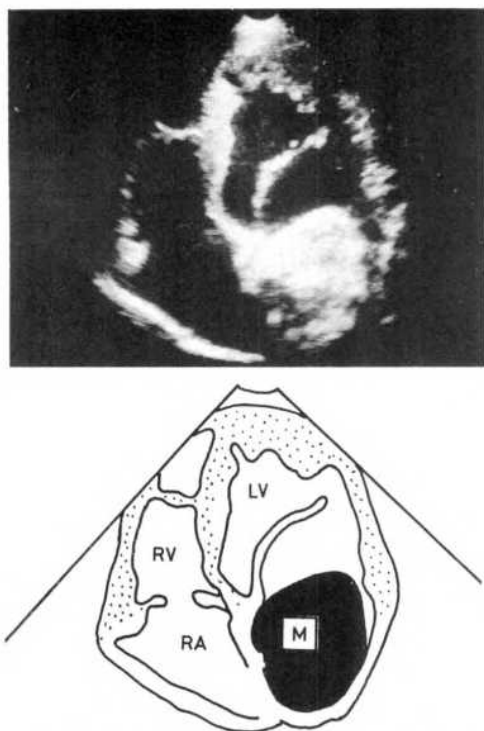


Fig 1 Cross sectional echocardiographic still frame image from the apical four chamber view of patient 1, showing a firm left atrial mass, remaining impacted in the left atrium during diastole with no clear determination of point of attachment. LV, left ventricle; M, myxoma; RA, right atrium; RV, right ventricle.

a routine visit for anticoagulation control he was found to have an erythrocyte sedimentation rate of 100 mm in the first hour. Cross sectional echocardiography showed an almost immobile mass the size of a tennis ball that was attached to the posterior left atrial wall (fig 1). A left atrial myxoma, 10 cm in diameter, was excised at operation. It had a broad (2 cm in diameter) very short stalk attached to the free wall of the left atrium adjacent to the superior pulmonary veins. This part of the atrial wall was also excised. Six months after operation the patient was fit and had returned to work.

CASE 2

In March 1979 a 41 year old woman, who had previously been well, had a fall associated with loss of consciousness. Over the next three years she was admitted to hospital on 25 occasions because of transient episodes of loss of consciousness. She suffered three episodes of hemiparesis involving the right side on one occasion and the left side twice. In April 1982 investigations including bilateral carotid arte-

riography, cerebrospinal fluid examination, computed tomography, and M mode echocardiography were all normal. Diagnosis included epilepsy, migraine, and hysteria. Several therapeutic treatments were tried without benefit. In August 1983 the patient attempted suicide.

In June 1984 she was referred to Hammersmith Hospital. Cardiovascular examination was unremarkable. Her mental state was normal but there was mild dysarthria and a spastic quadriplegia. The erythrocyte sedimentation rate was 45 mm in the first hour, haemoglobin 12.2 g/dl, and the biochemical profile was normal. The total protein concentration was 61 g/l, albumin was 41 g/l, and immunoglobulins were normal. C reactive protein was raised (55 mg/l); there was no complement consumption. Tests for rheumatoid factor and auto-antibodies were negative. Chest x rays and the electrocardiogram were normal. Cross sectional echocardiography showed a relatively large highly mobile mass attached to the posterior left atrial wall and protruding into the left ventricle in diastole (fig 2). A left atrial myxoma was diagnosed and in June 1984 the tumour was successfully excised. The left atrium contained a 4 cm diameter classic myxoma of the very friable frogs egg type (fig 3). It was attached by a thin stalk to the left atrial wall, just below the right inferior pulmonary vein. Both the atrioventricular valves were normal. The post-operative period was uneventful.

CASE 3

A 33 year old man was admitted from casualty in a comatose state after a sudden collapse. Fundoscopy showed attenuation of the blood vessels of the left eye but no papilloedema or haemorrhages. Cardiovascular examination was normal and peripheral pulses were all present. Laboratory data showed a white blood count of $19.4 \times 10^9/l$ and the erythrocyte sedimentation rate was 75 mm in the first hour. The total serum protein concentration was 76 g/l. Serum protein electrophoresis and quantitative immunoelectrophoresis showed a small increase in the γ region; IgA and IgM concentrations were normal. The IgG concentration was slightly raised with no paraprotein band. The concentration of C reactive protein was raised (38 mg/l). Cerebrospinal fluid was normal with a pressure of 14.5 cm. Chest and skull x rays, electrocardiogram, and a tomographic scan of the brain were all normal.

Six hours later the patient was noted to have cold and pale legs with absent pulses. Cross sectional echocardiography was then performed and a rather small but highly mobile mass attached to the left side of the atrial septum was identified (fig 4). Urgent embolectomy via the right femoral artery recovered

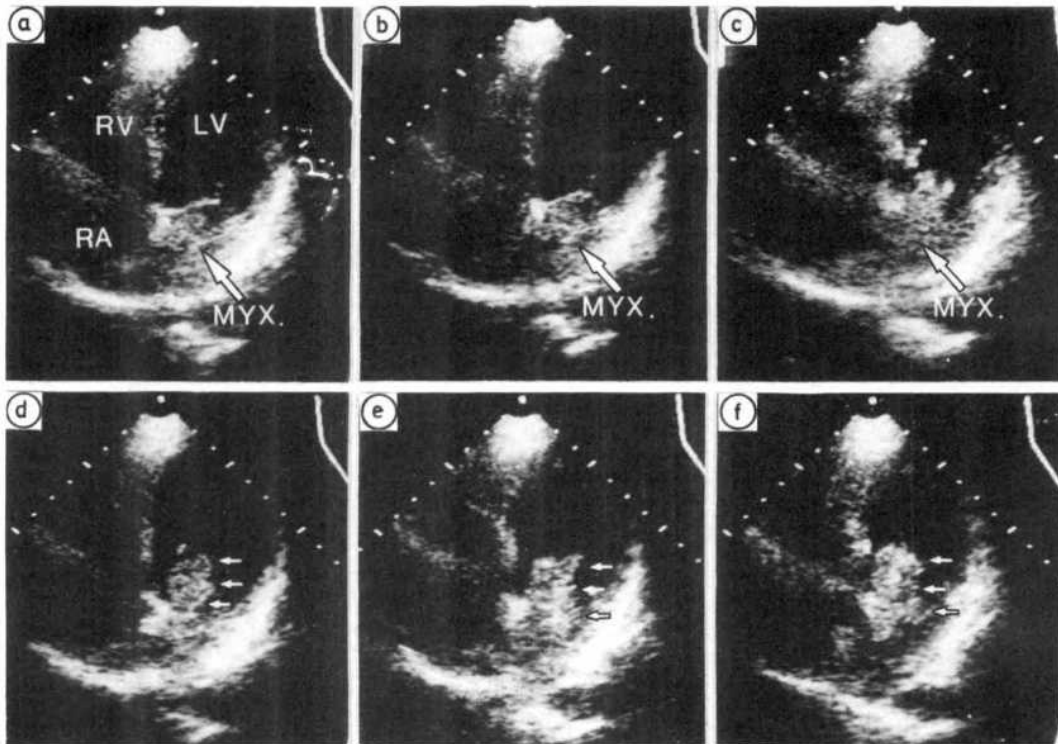


Fig 2 Cross sectional echocardiographic image from the apical four chamber view of patient 2. Sequential views throughout the cardiac cycle demonstrate the myxoma (arrows) within the left atrium (a, b), engaging the mitral valve (c), and protruding into the left ventricle in diastole (d, e, f).

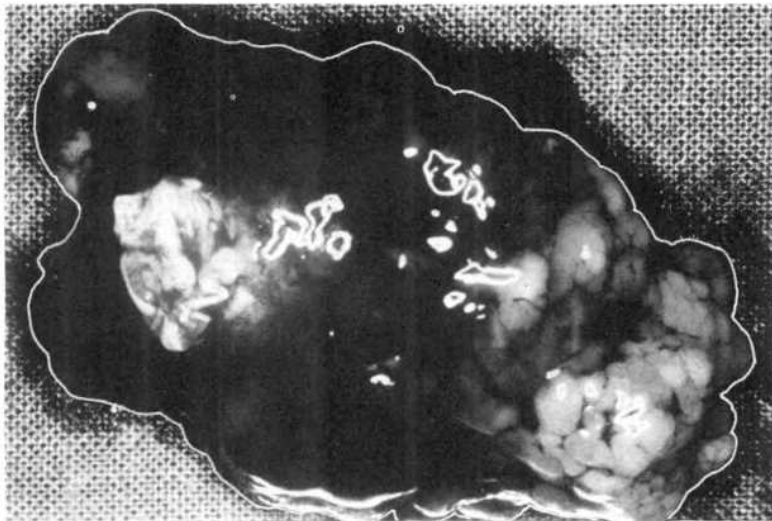


Fig 3 Photograph of the myxoma removed from patient 2. It measured 4.0 x 3.0 cm.

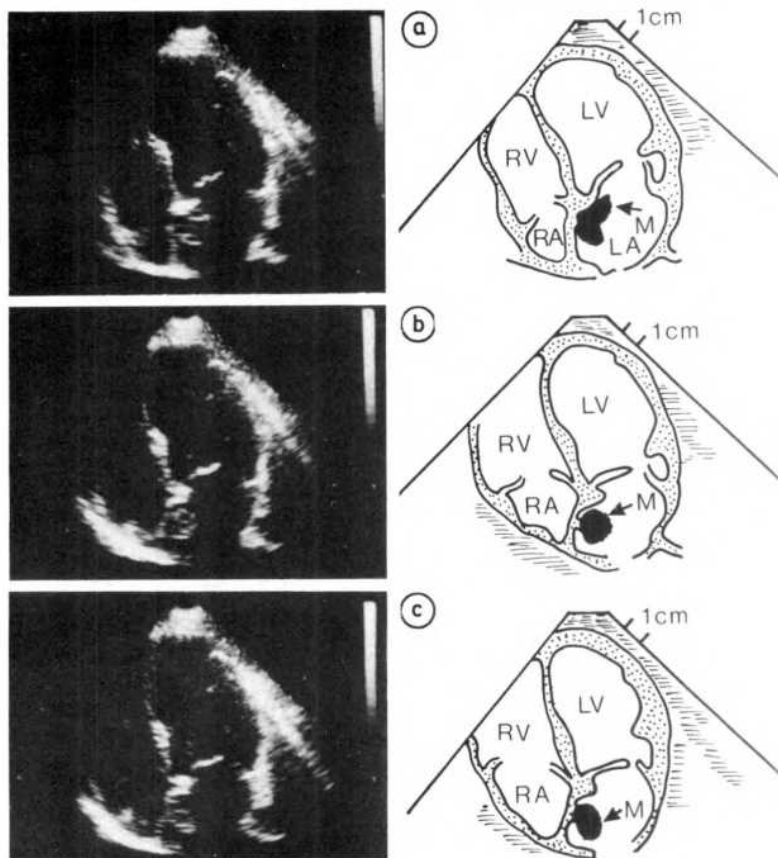


Fig 4 Echocardiogram taken from the apical four chamber view in diastole (a) mid-systole (b), and late systole (c) in patient 3. The small myxoma (M) moved along the left atrial side of the atrial septum without engaging the mitral valve. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

a saddle embolus consisting of myxomatous tissue. The arteries to both legs were occluded. A 55 cm stratified embolus with alternating layers of myxoma tissue and thrombus was removed from the right femoral artery. Because of severe brain damage thoracotomy was not attempted and the patient subsequently died.

Necropsy confirmed the presence of embolised myxoma tissue and thrombus both in the legs and carotid arteries. There was a sessile left atrial myxoma, which measured 2.5 cm in its largest diameter, attached to the fossa ovalis (fig 5). The mitral valve showed roughening and thickening consistent with erosion by a much larger tumour. Microscopy of the tumour showed that it was avascular and relatively hypocellular with a very loose matrix and without any definite capsule; this meant that the tumour was extremely friable (fig 6).

Discussion

Atrial myxomas can mimic almost any cardiovascular disorder and they may produce symptoms and signs that direct attention away from the heart.⁹⁻¹⁶ The clinical features can best be considered as obstructive, resulting from occlusion of the mitral valve orifice, embolic, or constitutional. The diagnosis of left atrial myxoma should be strongly suspected when this triad is present¹¹; however, when as in our patients there are no signs of left ventricular inflow tract obstruction the diagnostic search may be directed away from the heart.

There are two distinct forms of cardiac myxomas.¹⁷ The first form is semitransparent gelatinous with a frog spawn appearance (patients 2 and 3) and may give rise to multiple systemic emboli. As a consequence such a myxoma may never become large



Fig 5 Postmortem photograph of the myxoma in patient 3 attached to the fossa ovalis. The myxoma measured 2.5×1.0 cm.

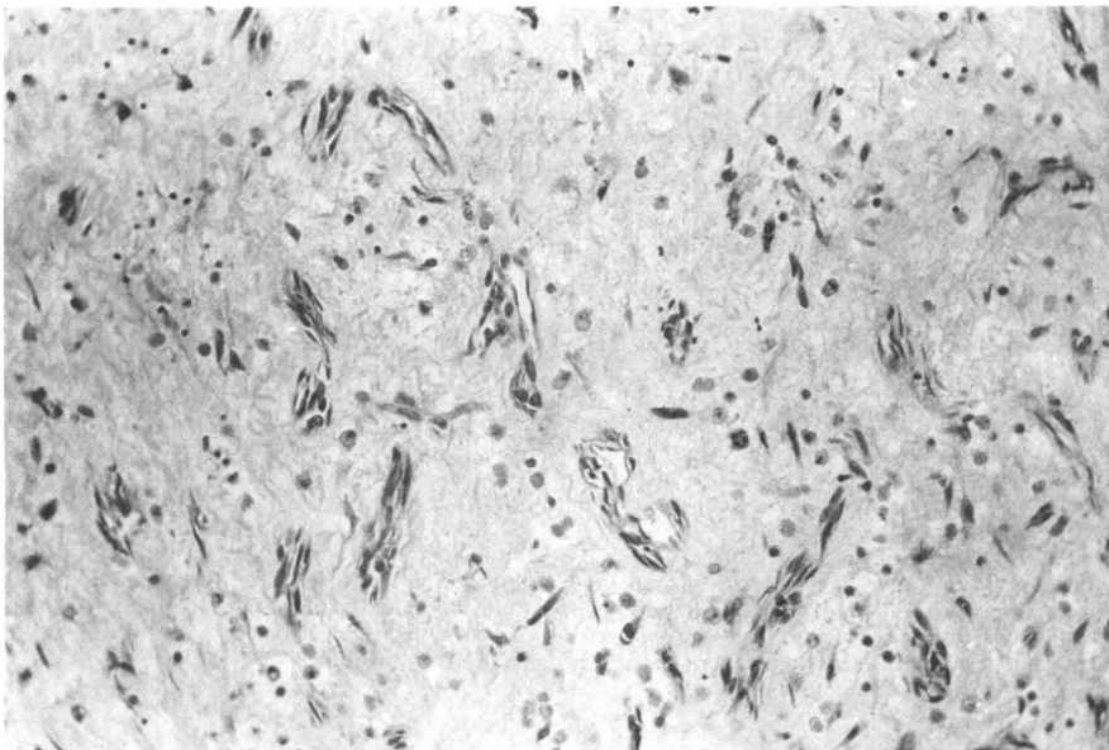


Fig 6 Photomicrograph of a section of the myxoma in patient 3 showing the lack of vascularisation and the generally hypocellular consistency of the tumour.

enough to produce haemodynamic effects or clinical murmurs. The second type of myxoma is much firmer and usually produces signs of left ventricular inflow tract obstruction that mimic mitral stenosis. The myxoma in patient 1 belonged to the second category but did not produce a murmur because the pedicle was too short and the tumour too large to engage the mitral valve orifice. The myxoma could have been present for a long time and may have been missed by both M mode echocardiography and cardiac catheterisation nine years before the correct diagnosis was made. In both types of myxoma constitutional disturbances may occur in association with anaemia, an increased erythrocyte sedimentation rate, and a variable increase in the concentration of plasma immunoglobulins. One explanation is that the microemboli from the myxomatous tissue, which contain mucopolysaccharides, may function as polyclonal activators of B lymphocytes irrespective of the immunoglobulin receptor on the B cell surface.¹⁸ The presumed mitogenic signal for T cell dependent antigens would be generated through the interaction of T cells with the antigen held on the surface of the B cell.¹⁹ The auto-antibodies produced reflect the characteristics of the population of myxoma cells and their fragments which react with the polyclonal activator. Other explanations such as impaired immune self-tolerance might also be feasible. All our patients had constitutional disturbance in association with high erythrocyte sedimentation rate, anaemia, and raised concentrations of C reactive protein.

Cross sectional echocardiography has made a great impact on the diagnosis of intracardiac masses and is more sensitive than M mode echocardiography.⁶ Its diagnostic accuracy arises from the ability to examine all four intracardiac chambers in several planes. This has made cardiac catheterisation, which is potentially hazardous²⁰⁻²² and delays surgery, both unnecessary, and unjustifiable. Moreover, unless a myxoma is specifically sought, "routine" right and left ventriculography may not reveal the tumour. This happened in the case of patient one. In patients 1 and 2 the diagnosis would have been further delayed or would not have been made before necropsy if echocardiography had not been performed.

Although cross sectional echocardiography permits the accurate determination of tumour size, the point of attachment, mobility, and consistency of the intracardiac masses,^{7,23} these features are not always enough to characterise the great variety of cardiac tumours or distinguish them from thrombi.⁸ In patient 1 the left atrial mass was not typical of a myxoma in that it was firm and sessile, not deformable, and only moved slightly during the cardiac

cycle. For these reasons it had been clinically silent. Fyke *et al* recognised similar echocardiographic appearances in five of their 20 patients with left atrial myxomas⁷; others have reported cases of malignant atrial tumours simulating myxoma echocardiographically.²⁴⁻²⁶

Surgical excision of cardiac myxomas should be performed without delay. In the Hammersmith experience there have been no recurrences.²⁷ Recurrences have been reported after incomplete excision or growth from a second pre-tumorous focus.^{28,29} Excision should therefore include a full thickness of atrial septum or wall surrounding the pedicle attachment and the defect created should be patched.

In conclusion, cross sectional echocardiography remains the technique of choice for demonstrating the presence of left atrial myxoma. A high degree of clinical suspicion, extending beyond patients who present with specific cardiological signs, is needed to ensure that these patients are referred for echocardiography. The occurrence of systemic emboli or the presence of constitutional signs with raised erythrocyte sedimentation rate and C reactive protein of unknown aetiology should be regarded as an indication for echocardiography.

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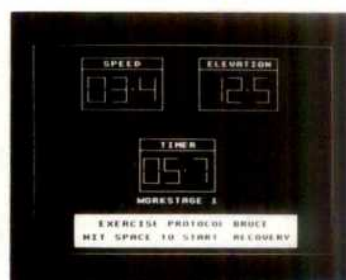
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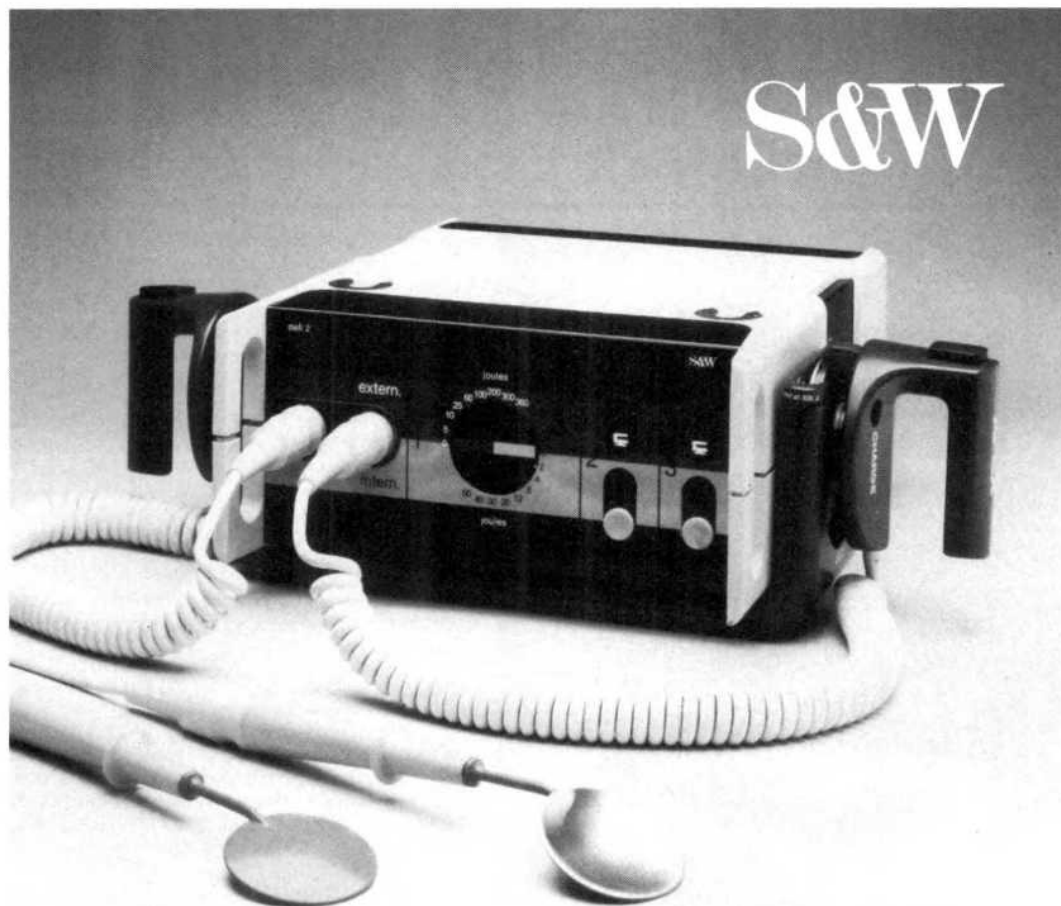


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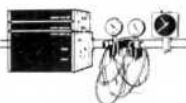
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Case reports

Infective endocarditis affecting the eustachian valve

A D EDWARDS, M A VICKERS, C J MORGAN

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SUMMARY A previously fit 44 year old man presented with acute staphylococcal pneumonia. Despite appropriate antibiotics he showed signs of continuing sepsis and eventually died. At necropsy endocarditis of the eustachian valve was found.

In the fetus the eustachian valve (valve of the inferior vena cava) directs blood flow preferentially from the inferior vena cava through the foramen ovale into the left atrium. In the adult it is redundant and usually rudimentary¹ although sometimes it is large enough to form a septum dividing the right atrium and creating cor triatriatum dexter.²

Infective endocarditis is known to complicate congenital heart anomalies but we are not aware of a previous description of endocarditis affecting the eustachian valve.

Case report

A 44 year old fireman who had no history of previous illness or intravenous drug abuse was admitted with right upper lobe pneumonia. Sputum repeatedly grew *Staphylococcus aureus* and he was treated with appropriate antibiotics. Over the next month the pneumonia progressed to a lung abscess, which discharged leaving a thin walled pneumatocele. During this time he had persistent hyperglycaemia and hyponatraemia and several episodes of septicaemia. Various organisms were cultured from blood and sputum and he was treated appropriately. His clinical condition did not improve despite discharge of pus and the continued use of antibiotics. An echocardiogram was performed which showed no evidence of endocarditis on the mitral, aortic, tricuspid, or pulmonary valves. A valve of the inferior vena cava was not specifically sought. Disseminated intravascular coagulation and acute renal failure devel-



The eustachian valve, covered with large vegetations, crosses the right atrium with its chordae tendineae extending above and below. The dark area, bottom right, is the orifice of the tricuspid valve; the oval fossa is evident above the eustachian valve.

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oped and he continued to deteriorate. He died seven weeks after admission.

Necropsy confirmed the pneumatocele and there was patchy interstitial fibrosis with alveolar type II cell hyperplasia throughout the lungs that was suggestive of a recent viral infection. In the right atrium there was a well developed eustachian valve and hanging from it were large vegetations (figure). There were also small sessile vegetations on the mitral valve cusps. The eustachian valve vegetations consisted of fibrin containing collections of neutrophils but no colonies of bacteria: we considered that they were likely to represent bacterial endocarditis sterilised by the antibiotics that had been administered throughout the patient's illness. The mitral valve vegetations consisted only of fibrin and appeared to be marantic lesions. The heart was otherwise normal. Diffuse intravascular coagulation, pituitary necrosis, renal cortical necrosis, and chronic pancreatitis were noted.

Discussion

A recent survey of infective endocarditis found that in 199 of 544 cases the site of infection within the heart was uncertain and in 171 of 541 cases no predisposing abnormality was identified.³ It was suggested that although a proportion may have had an unrecognised pre-existing valve lesion, in most the heart was normal. In our case we found an abnormality that may be the site of endocarditis in seemingly normal hearts.

Echocardiography is a valuable investigation in the patient with suspected endocarditis and when it is performed the major heart valves are always carefully examined. Right atrial structures such as the eustachian valve and the Chiari network can be visualised well by cross sectional endocardiography.^{2,4} The present case suggests that when bacterial endocarditis is suspected and the four major valves are examined and appear normal, a valve of the inferior vena cava may be present. If a eustachian valve is visualised echocardiographically it should be considered as a rare site for vegetations.

We thank Professor R H Anderson, Professor B Corrin, and Dr Y Ho for their advice.

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Staged septation of double inlet left ventricle

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From the *Royal Liverpool Children's Hospital, and †Saint Mary's Hospital, Manchester

SUMMARY Complete septation of a double inlet left ventricle with left anterior subaortic outlet chamber was carried out successfully as a staged procedure during the first two years of life in a patient with severe pulmonary hypertension and an abnormal left atrioventricular valve. In contrast with isolated pulmonary artery banding, which rarely has led to a satisfactory septation or modified Fontan operation, this technique achieved good initial palliation and uncomplicated intracardiac repair. It should be considered for infants with univentricular atrioventricular connection, two atrioventricular valves, and excessive pulmonary blood flow.

Although theoretically attractive,¹ septation of the univentricular heart during infancy has been hindered by technical difficulties in securing the prosthetic patch and frequent postoperative heart block. Ebert recently demonstrated in five infants with "common ventricle" that two Teflon patches without a pressure difference across them could be positioned accurately with a few sutures, and that over a period of 5-8 months they became firmly adherent to the endocardium.² This avoided injury to the conduction system and created a stable base to which a third patch was attached, completing the prosthetic septum. The following case illustrates successful extension of this concept to a patient with double inlet left ventricle and subaortic outlet chamber.

Case report

A baby girl weighing 5.5 kg was first seen at six months of age during emergency hospital admission for a chest infection. She was said to have been normal at full term delivery in Iran but had failed to thrive. A heart condition was diagnosed when she was three months old.

On examination, the infant was pyrexial, tachypnoeic, and mildly cyanosed with clubbing. Bounding pulses at a rate of 160 beats per minute were present throughout. Enlargement of the heart with a thrill along the left sternal edge was detected by palpation. In addition to a loud systolic murmur, auscultation disclosed a single, accentuated, second heart

sound. The liver was enlarged, and both lungs had diffuse crepitations. Chest x ray showed cardiomegaly with plethoric lung fields. The electrocardiogram had a vertical-axis and dominant left ventricular forces. Cross sectional echocardiography showed a large chamber of left ventricular morphology that received both atrioventricular valves and gave off the pulmonary artery. The aorta arose from a left-sided outlet chamber. The left atrium was dilated and the left atrioventricular valve appeared to be thickened.

The patient's heart failure responded to treatment with digoxin and diuretics, and gram negative pathogens in the urine and sputum were cleared with antibiotics, such that cardiac catheterisation could be performed ten days after the start of treatment. This confirmed the echocardiographic diagnosis and showed pulmonary hypertension, with pressures in the ventricle and ascending aorta being 83/6 mm Hg and 83/49 mm Hg, respectively, and in the main pulmonary artery 64/31 mm Hg. Mean left atrial pressure was 15 mm Hg compared with 5 mm Hg in the right atrium, and pulmonary vascular resistance was 3.2 units.m². Pulmonary flow was two and a half times systemic, and systemic arterial saturation was 91%.

Although cardiac failure was controlled, the infant failed to gain weight and remained ill. She was admitted to hospital with repeated chest infections. A second catheterisation at 14 months showed virtually equal systemic and pulmonary blood flow, with a pulmonary resistance of 10.9 units.m² in air, falling to 2.1 units.m² in 100% oxygen.

First stage septation and pulmonary artery banding were performed when she was 15 months old and

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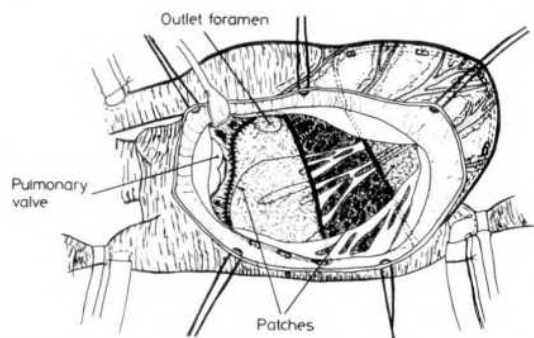


Fig 1 Surgical view of the first stage operation. The ventricle is exposed through the right atrium by retraction of the right atrioventricular valve. The left atrioventricular valve and outlet foramen lie behind the upper Teflon patch, while the lower patch separates the tensor apparatus of left and right atrioventricular valves.

weighed 6.7 kg. The left atrioventricular valve, inspected on cardiopulmonary bypass through an enlarged patent foramen ovale, was found to be thickened but adequate in size. Exposure was set up through the right atrioventricular valve, and a patch of Teflon felt was positioned between the two inlet valves, the outlet foramen, and the pulmonary artery with a continuous suture (fig 1). In the region of the conduction system, stitches were taken inside the upper margin of the outlet foramen.³ A second, triangular patch was attached at the apex of the ventri-

cle with interrupted mattress sutures supported by Teflon pledgets outside the heart. After the patient had come off bypass the diameter of the pulmonary artery was reduced to about 7 mm by banding. Together, the patches constituted approximately 75% of a ventricular "septum".

Cardiac function was excellent in the immediate postoperative period while the patient was on 0.1 µg/kg/min isoprenaline. Systolic arterial blood pressure was 100–110 mm Hg and she was in sinus rhythm. The patient later suffered transient supra-ventricular tachycardia which was controlled by rapid atrial pacing, and fever with seizures, attributed to pseudomonas infection of the sputum and urine. Despite this she was extubated on the third postoperative day and made an otherwise uneventful recovery.

During the next six months she grew well without signs of heart failure or respiratory infection. Cardiac catheterisation five months after operation showed satisfactory banding of the pulmonary artery, with a distal pressure of 22/11 mm Hg and pulmonary resistance of 2.9 units.m². The patches were both in a good position, but there was an 8 mm Hg gradient across the outlet foramen, which appeared to be restrictive on both echocardiography and angiography (fig 2).

At the time of her second open heart operation, in February 1986 the patient was 22 months old and weighed 9.6 kg. The previously inserted Teflon was found to be completely endothelialised and firmly

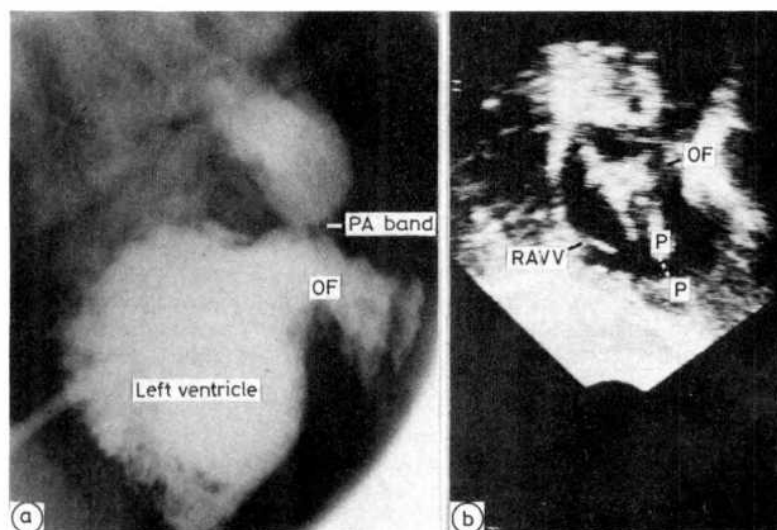


Fig 2 Left ventricular angiogram (a) and echocardiogram (b) after first stage septation and pulmonary artery banding. The dotted line between P and P indicates position of third patch, which later completed the ventricular partition. OF, outlet foramen; PA, pulmonary artery; RAVV, right atrioventricular valve; P, septation patches.

adherent to the ventricular endocardium. The outlet foramen was enlarged by excision of a wedge of muscle from the posterior inferior trabecular septum, the pulmonary artery was debanded, and septation was completed by transatrial insertion of a third Teflon patch.

Postoperatively the patient remained in sinus rhythm. A transient increase of left atrial pressure from 12 mmHg to 20 mmHg was treated by inotropic support (5 µg/kg/min dobutamine) and afterload reduction (glyceryl trinitrate). Extubation was performed uneventfully on the second day after operation, and the patient was discharged from hospital one week later. Doppler echocardiography before discharge showed no clinically important gradient across the pulmonary artery or outlet foramen or any shunt across the prosthetic septum. There was a trace of regurgitation through the left atrioventricular valve. Ventricular contractility was good and movement of the septal patches was minimal.

Discussion

Prognosis is generally poor in patients with double inlet ventricle. Of those presenting in the first year of life, successful "correction" by ventricular septation or a modified Fontan operation was achieved in <2% of one series⁴; while in another, half of those who survived to childhood and did not undergo surgery died within fourteen years of diagnosis.⁵ Appropriate surgical intervention has been shown to improve both the length and quality of life for these patients,^{1,6} but management of those with increased pulmonary blood flow continues to be difficult.

Many in this subgroup develop cardiac failure and pulmonary hypertension with respiratory infections and failure to thrive early in life. Banding of the pulmonary artery can be done with a low operative risk⁷ and ten year actuarial survival is 74%⁶; but even after haemodynamically effective banding, pulmonary vascular structure may remain abnormal and later prejudice the outcome of a Fontan procedure.^{8,9} Although subtle structural anomalies and even moderately increased pulmonary arterial resistance are tolerable with the septation operation, loss of ventricular compliance, outlet foramen obstruction, small ventricular size, and intrapericardial adhesions all significantly increase early mortality after septation^{1,6} and may be caused or accentuated by banding.^{10,11}

Insertion of two patches within the ventricle combined with pulmonary artery banding for a limited period appears to be a safe and effective means of palliation that also facilitates definitive septation. Our patient differed from those reported by Ebert in having a more common type of double inlet ventricle

(that is both atria were connected to a dominant left ventricle with a left sided, anterior rudimentary right ventricle), raised pulmonary vascular resistance, and an abnormal left atrioventricular valve. These latter two factors almost certainly would have precluded a successful Fontan operation in the future. None the less, both stages of septation were followed by a relatively uneventful post-operative convalescence. In retrospect, it would have been better to perform the first stage septation and pulmonary artery banding after the initial investigation, because the operative risk increased with the subsequent considerable rise in pulmonary vascular resistance. Because the hazards of cardio-pulmonary bypass may be greater in very young infants,¹² it would be reasonable to carry out isolated pulmonary artery banding if operation were required during the first two or three months of life, particularly for associated coarctation of the aorta. The initial stage of septation could then be undertaken between three and six months of age. To delay protection of the pulmonary vasculature for more than eight months probably increases the likelihood of permanent changes in the lungs,¹³ and accordingly palliation should start before this time.

There are several important unanswered questions about this procedure. It is not known whether outlet foramen obstruction will recur. The fate of atrioventricular valves in a growing heart whose inlet to apex length is fixed, the incidence of thromboembolic complications during patch endo-thelialisation, and the late results as regards ventricular function and cardiac rhythm are uncertain. Early survival and functional results have been encouraging, however, and they support the continued development of techniques for septation in infants with suitable ventricular morphology and excessive pulmonary blood flow.

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Coincidence of true and false left ventricular aneurysms after myocardial infarction

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SUMMARY False aneurysm of the left ventricle is a rare complication of myocardial infarction. In this case cross sectional echocardiography demonstrated the presence of both true and false left ventricular aneurysms. This was confirmed at operation when both aneurysms were successfully resected.

A false aneurysm or pseudoaneurysm is a contained myocardial rupture, its wall being lined by pericardium and mural thrombus.¹ It is a rare complication of myocardial infarction.² In contrast with true ventricular aneurysm it has a tendency to rupture and therefore requires operation.³

Previous reports have demonstrated the value of cross sectional echocardiography in distinguishing true aneurysms from false aneurysms.⁴ True and false aneurysms rarely coexist and when they do the diagnosis may not be apparent. We report on a case that was diagnosed before operation.

Case report

A 70 year old man sustained an anterolateral myocardial infarction in May 1984. He made an uneventful recovery and was discharged well. He was readmitted two months later complaining of a deterioration in his breathing over the previous 48 hours. He had also noticed a pleuritic retrosternal chest pain. On examination he was in left ventricular failure with a sinus tachycardia of 120 beats per minute, blood pressure 110/70 mm Hg, and bilateral basal crepitations. His apical impulse was dyskinetic and displaced laterally and inferiorly.

His electrocardiogram showed ST segment elevation in leads V2 to V6, which was similar to the pattern seen when he was discharged from hospital. A chest radiograph showed pulmonary oedema, and a new shelf on the left border of the heart shadow consistent with a ventricular aneurysm. Pulmonary oedema responded to diuretics.

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Echocardiography showed a large aneurysmal region at the apex of the left ventricle (fig 1). There appeared to be a "septum" separating the most apical part of the aneurysm from the left ventricle. This "septum" moved towards the body of the left ventricle in systole, suggesting that the distal segment was expanding. No connection could be identified between this cavity and the rest of the left ventricle and it was taken to represent a false aneurysm.

Angiography demonstrated a connection between the left ventricle and the apical chamber as well as a true left ventricular aneurysm. At operation the

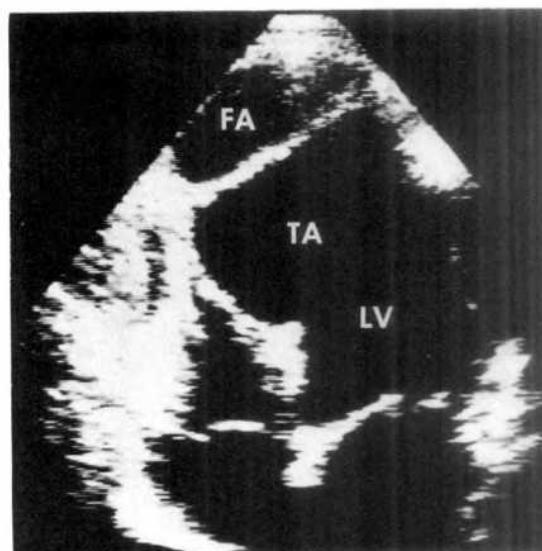


Fig 1 Cross sectional echocardiogram in the apical four-chamber view showing the following structures: false aneurysm (FA), left ventricle (LV), and true aneurysm (TA).

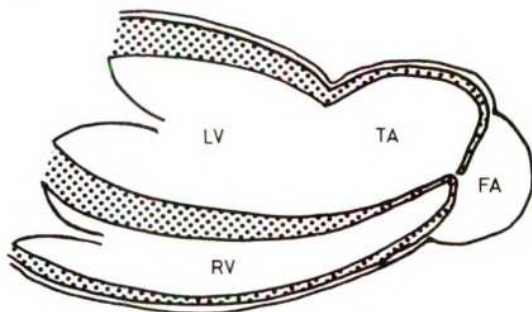


Fig 2 Diagrammatic representation of the intraoperative findings. LV, left ventricle; RV, right ventricle; TA, true aneurysm; FA, false aneurysm.

findings were confirmed. There was an apical true left ventricular aneurysm with a false aneurysm separated by a thin membrane (fig 2). Both aneurysms were resected. Six months after operation he was symptom free with normal exercise tolerance.

Discussion

A false aneurysm of the left ventricle is rare. It most commonly follows myocardial infarction but may also occur as a sequel to cardiac operation, trauma, or endocarditis.² It is a contained myocardial rupture and its walls consist of pericardium and thrombus. The complications of false aneurysm are similar to those of true aneurysm except for the important fact that they tend to rupture.⁵ Therefore, false aneurysm should be treated by early operation irrespective of the patient's symptoms.

True and false aneurysms may be distinguished by echocardiographic⁶ and angiographic findings.⁷ Cross sectional echocardiography is now established as a reliable method of demonstrating the major distinguishing feature of a false aneurysm—a neck that is narrower than the fundus of the aneurysm.⁴

In our case the false aneurysm was superimposed on a true aneurysm—a rare combination. The diag-

nosis was suspected principally because of the most unusual mobile band that separated the distal part of the left ventricle from the body of the ventricle. This could not be explained as a true aneurysm and no orifice could be seen despite a careful search in several views. At operation the thin septum proved to be thin infarcted myocardium and a small orifice was found. We have been unable to find similar descriptions of these distinctive echocardiographic findings, which presumably resulted from the development of a false aneurysm through the wall of a true aneurysm, the thin band being part of the original wall of the true aneurysm.

We thank Mr Graham Leech for his comments on the echocardiogram.

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Abnormal diastolic movement of the interventricular septum caused by a prolapsing right atrial myxoma

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From the Regional Adult Cardiothoracic Unit, Broadgreen Hospital, Liverpool

SUMMARY A 40 year old woman with cough and exertional dyspnoea was found to have a large right atrial myxoma by M mode and cross sectional echocardiography. Prolapse of the tumour into the right ventricle occurred during diastole with sufficient force to cause mechanical distortion of the interventricular septum. Septal motion became normal after surgical resection of the myxoma.

Right atrial myxomas rarely occur. The clinical findings are diverse and echocardiography is the single most useful investigation in confirming the diagnosis. In the present case the characteristic echocardiographic signs were accompanied by abnormal diastolic distortion of the interventricular septum caused by the impact of a large and highly mobile tumour.

Case report

A 40 year old woman presented with a five month history of non-productive cough and progressive exertional dyspnoea. She had been treated for anaemia three months before presentation. On examination the jugular venous pressure was raised 7 cm with a prominent "a" wave and positive Kussmaul's sign. The pulse was 80 beats/minute, sinus rhythm; and blood pressure was 130/90 mm Hg. A loud third heart sound (tumour plop) was followed by a long low pitched mid-diastolic murmur with presystolic accentuation and both were increased in intensity by inspiration.

The following laboratory results were noted: haemoglobin 12.5 g/dl, white blood cell count $9.1 \times 10^9/l$, erythrocyte sedimentation rate 40 mm in first hour, total protein 80 g/l (normal 57-77),

albumin 44 g/l (35-47), C-reactive protein 37.7 mg/l (normal <18.0), IgM 2.8 g/l (normal 0.7-2.5), total bilirubin 21 $\mu\text{mol/l}$ (normal 0-18), alkaline phosphatase 121 U/l (normal 10-110), aspartate transaminase 234 U/l (normal 10-30), lactate dehydrogenase was normal.

The electrocardiogram, chest radiograph, and pulmonary function tests were normal. Phonocardiography confirmed the clinical findings. M mode echocardiography demonstrated a mass of echoes behind the tricuspid valve; these filled the right ventricular chamber during diastole and produced paradoxical posterior bulging of the interventricular septum. The abnormal echoes disappeared during ventricular systole (fig 1). Cross sectional echocardiography demonstrated a large mobile pedunculated tumour mass in the right atrium which originated from the interatrial septum and prolapsed into the right ventricle in diastole distorting the interventricular septum (fig 2). The right atrium and ventricle were dilated and the left atrium and ventricle were normal. The right atrial pressure trace showed striking "a" waves reaching 16 mm Hg with a mean pressure of 12 mm Hg. Contrast injection into the superior vena cava confirmed the echocardiographic diagnosis of prolapsing right atrial myxoma and showed patent right and left pulmonary arteries. A perfusion lung scan was normal.

At operation a large gelatinous globular mass ($8 \times 6 \times 5$ cm) with an haemorrhagic surface filled the right atrium. Its broad base originated from the fossa ovalis and the tumour prolapsed into the right ventricle. It was successfully removed. Histology confirmed the tumour to be a benign atrial myxoma.

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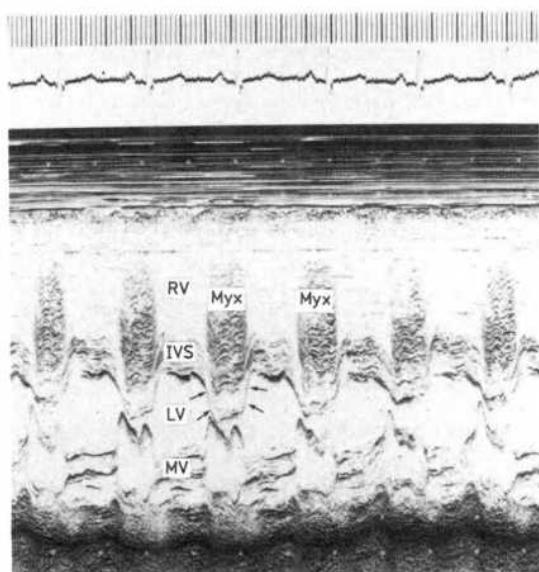


Fig1 M mode echocardiogram showing a cloud of echoes from a prolapsing right atrial myxoma (Myx). The echoes fill the right ventricular chamber (RV) during diastole and disappear during ventricular systole. The interventricular septum (IVS) is displaced posteriorly (arrows) in diastole by the large prolapsing tumour mass. LV, left ventricle; MV, mitral valve.

The patient made an uneventful recovery and subsequent echocardiography demonstrated normal interventricular septal motion.

Discussion

About a third to a half of primary cardiac tumours are myxomas. Ninety per cent occur in the atria but only about 20% are found in the right atrium.¹⁻³ The symptoms and physical signs of right atrial myxoma are diverse.⁴⁻⁶ Echocardiography is the most sensitive non-invasive method for detecting right atrial myxomas and for excluding a concomitant left atrial myxoma.^{5,7} The tumours typically appear as a dense cloud of echoes behind the tricuspid or mitral valves. Cross sectional echocardiography allows additional assessment of tumour size and mobility, including the detection of myxomas too small or not sufficiently mobile to prolapse through the tricuspid valve, differentiation of myxoma from infective vegetations on the tricuspid valve,⁸ and the presence of haemodynamically important tumour emboli in the right and left pulmonary arteries.⁹

An additional and striking echocardiographic sign was noted during cross sectional examination of our patient that was consistent with a large and highly

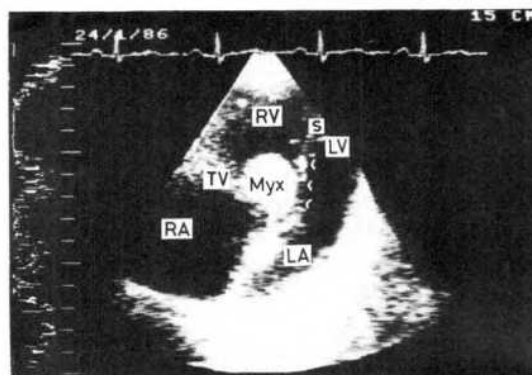


Fig2 Cross sectional echocardiogram of apical four chamber view showing diastolic distortion (arrows) of the interventricular septum (s) by a large prolapsing right atrial myxoma (Myx). RA, right atrium; RV, right ventricle; TV, tricuspid valve; LA, left atrium; LV, left ventricle.

mobile tumour. Rapid diastolic excursion of the mass through the tricuspid valve and into the right ventricle was arrested by its sudden impact against the upper interventricular septum; this caused the septum to bulge posteriorly towards the left ventricle. The M mode appearance of this event thus simulated reverse or "paradoxical" motion of the interventricular septum. The association of "paradoxical" septal motion and right atrial myxoma has been noted in two previous case reports. Goldschlager *et al* described right atrial myxoma presenting as congenital heart disease with a right to left shunt; paradoxical septal motion during systole with a normal right ventricular dimension was present but its cause was unexplained.¹⁰ Right ventricular enlargement and paradoxical septal motion in systole were attributed by Yuste *et al* to the right ventricular volume overload of tricuspid regurgitation due to the presence of a large right atrial myxoma, although the abnormal septal motion persisted after its removal.¹¹ In our case the primary abnormality of septal motion occurred in diastole and septal motion became normal after removal of the tumour. This case demonstrates that the impact force of a large mobile right atrial myxoma is sufficient to distort the normal shape of the interventricular septum, a substantial structure. Massumi has described the diagnosis of large mobile right heart myxomas through detection of palpable tumour shocks and audible plops as the tumour is hurled vigorously against intracardiac structures in various phases of the cardiac cycle.⁶ Even when these physical signs are not detectable mechanical distortion of intracardiac structures may represent their echocardiographic counterpart.

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Fatal heart block due to mesothelioma of the atrioventricular node

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SUMMARY A fit young man of 23 was symptom free until the time of his death despite a narrow complex complete heart block, with resting heart rates down to 35 beats/min, that was first diagnosed when he was 10. The clinical diagnosis remained congenital heart block. Necropsy showed extensive infiltration of the atrioventricular node and proximal bundle by mesothelioma tissue. Pacing had not been advised because of his excellent exercise tolerance.

When not associated with other congenital cardiac abnormalities, complete heart block diagnosed early in life is compatible with a responsive cardiac output and long term survival.^{1,2} The individual patient's prognosis cannot be known with certainty³ and symptoms such as syncope or impaired effort tolerance are the usual indications for pacing,⁴ there being an increased incidence of these symptoms after the age of 30 years.^{5,6}

McHenry noted a progressive decrease in resting heart rate as these patients grow older,⁷ persistent resting rates of 50 beats per minute or less being associated with syncope in children and young adults.⁸ The subject of this report had resting bradycardia of that order but remained symptom free with a better than average working capacity right up to the time of his unexpected death.

Case report

Complete heart block with narrow QRS complexes and a resting bradycardia of 41 beats per minute was first reported when he was 10 years old. His parents were alive and well. Clinical accompaniments were cannon waves, a forceful apex beat, and a pulmonary ejection murmur of moderate intensity. Anti-streptolysin O, toxoplasma, and viral titres were normal. He was referred for cardiological assessment at the age of 15 years because associated hypertrophic cardiomyopathy was suspected. M mode echocardiography showed no asymmetry. The left ventricular free wall was 20 mm thick and the septum was 18 mm, with normal chamber dimensions and

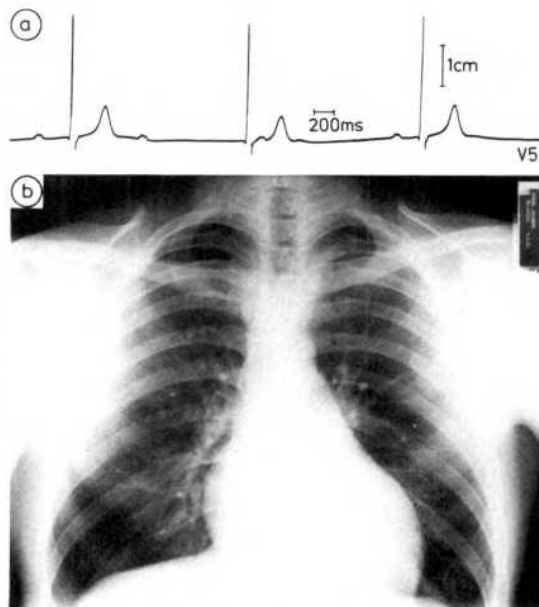


Fig 1 (a) Electrocardiogram recorded at age 20 years. (b) Chest x ray at 23 years.

valve appearances. At that time his right brachial blood pressure was 110/55 mm Hg and his heart rate was 42 beats per minute at rest, readily increasing to 64 beats per minute (without extrasystoles) on light exercise. He was accustomed to strenuous exercise including football and wrestling.

An electrocardiogram (fig 1) recorded in 1982, when he was 20 years old, confirmed complete heart block with narrow QRS complexes, the atrial rate

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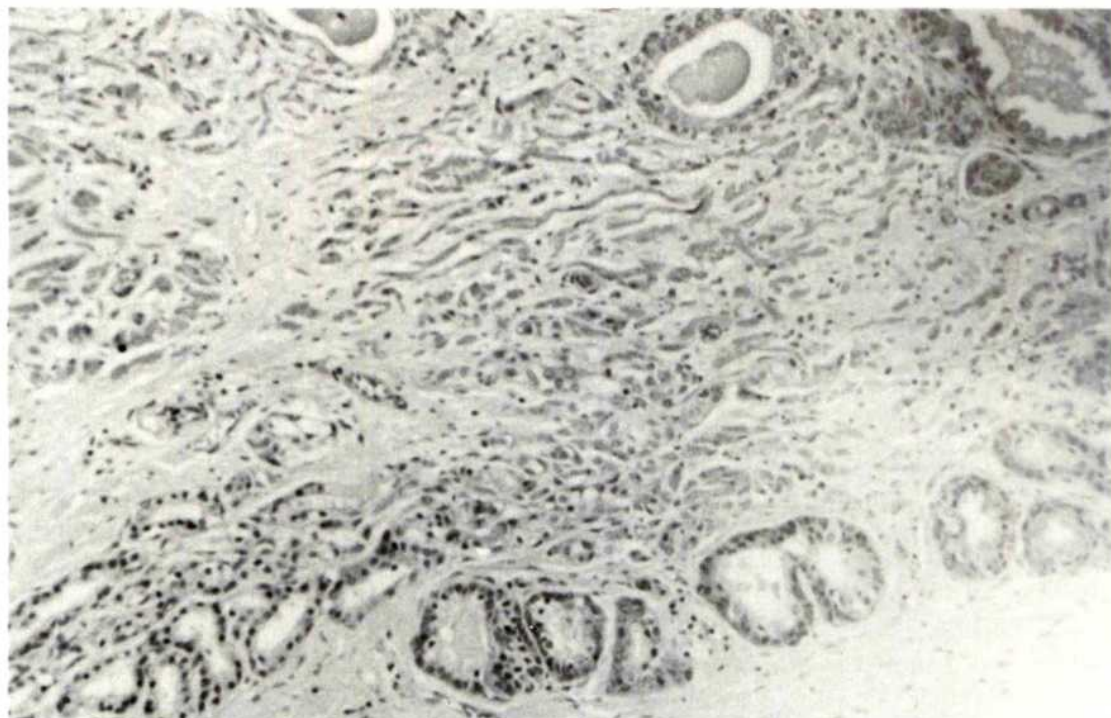


Fig 2 Photomicrograph of part of the atrioventricular node which is permeated and surrounded by mesothelioma tubules and cysts. A fibrous atrioventricular ring is present (bottom right). Haematoxylin and eosin.

showing considerable variation with constancy of the ventricular rate at 35 beats per minute. QTc was 350 ms. The S waves in V2 measured 30 mm. Chest x ray showed a bulky cardiac outline with a normal transverse cardiac diameter (140 mm).

He remained very fit, working as a farm labourer, and reported no dizziness or effort related symptoms at the time of his last review in April 1985. He was then aged 23 years (height 1.85 m and weight 79.5 kg). His resting heart rate was 40 beats per minute and systolic blood pressure 90 mm Hg. The transverse cardiac diameter on x ray (fig 1) was 168 mm.

In May 1985 he loaded a lorry with bales of straw and set off in it, chatting happily. Three or four minutes later he complained of central chest pain, writhed "for a few moments", and died. He had not appeared to be dyspnoeic.

PATHOLOGICAL EXAMINATION

At necropsy the only gross abnormalities were pulmonary oedema, pericardial adhesions, and an apparently enlarged heart. The heart weight (560 g) was substantially in excess of the upper figure (372 g) for a 79 kg man cited by Ludwig (1979)⁹ and the limit of 399 g for a 1.90 m man given by Olsen

(1980)¹⁰; though Hangartner *et al* (1985) give an upper 95% confidence interval of 584 g for a normal 80 kg man.¹¹ The adhesions were confined to the region of the mid-anterior interventricular groove, the underlying vessels and myocardium being normal. The posterior interatrial septum was slightly thickened by pale soft tissue. The right ventricle and valves were normal. On the left side the atrium, mitral, and aortic valves were normal. The left ventricle was hypertrophied with the thickness of the free wall varying from 18 to 20 mm. The septum was 18 mm thick with mild milky white thickening of the endocardium over the flat basal region.

The atrioventricular node, bundle of His, and proximal bundle branches were dissected out en bloc and serially sliced every 2–3 mm. These eight blocks were each cut on their inferior (posterior) faces. Eighteen further blocks were examined, three from the atria, two from the interventricular septum, five from the left ventricular free wall, five from the free wall of the right ventricle, and three that combined myocardium and descending coronary arteries. Electron microscopy was not undertaken because of the interval between death and necropsy and the fact that the heart had been fixed in formol saline before receipt by PGIS.

Microscopically there was extensive infiltration of the atrioventricular node and proximal bundle by gland-like mesothelioma tissue (fig 2). This infiltrate was also separating the node from the atrial myocardium. The endocardium of both ventricles was slightly thickened and contained strands of smooth muscle, indicating some degree of longstanding dilatation. The left ventricular muscle was slightly hypertrophied with myocytes up to 25 µg diameter and there was no myocyte disarray. As well as old epicardial adhesions there was some epicardial lymphocytic infiltrate.

Discussion

The clinical diagnosis was congenital heart block and there is no means by which it could have been refined. None of the 50 or so reported cases of mesothelioma of the atrioventricular node has been diagnosed in life.¹² The decision not to implant a pacing system was based on the notion that asymptomatic congenital heart block carries a good prognosis and that when sudden death occurs it may be due to ventricular tachycardia or fibrillation.¹²

The mode of death in this case was not unheralded syncope but appears to have been consistent with ventricular tachycardia during the recovery period after strenuous exertion—a possibility indicated by Cobbe.⁴ It may be that formal exercise testing would have shown a tendency to ventricular extrasystoles^{7,8,13} and it is possible that pacing with a dual chamber or other rate-responsive system would have reduced or abolished it. It may also be that pacing should have been offered because of the clinical, electrocardiographic, radiographic, and echocardiographic indications of left ventricular hypertrophy. In the absence of cardiomyopathy, it is possible that such a system would, over the years, have limited cardiac hypertrophy to a degree that was compatible with the patient's demands for a high cardiac output on exercise and would have afforded some protection against myocardial instability caused by bradycardic underperfusion during the post-exertional phase.

It is most unlikely that the recurrent mild pericarditis played any part in this man's death. None of the multiple sections of the area of the mesothelioma showed any acute event such as a haemorrhage or rupture of a cyst that might have triggered a ventricular tachycardia.

The mesothelioma or adenomatoid tumour of the heart has been recognised as a cause of heart block

since the report of Armstrong and Monckeberg in 1911.¹⁴ McAllister has described it as the smallest tumour capable of causing sudden death,¹⁵ though the time course from its origin (before birth) to death may extend over many years.

We thank Dr T D Marsh and Dr J E Trowell for information essential to the compilation of this report.

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Correspondence

Unexpected myocardial disease in patients with life threatening arrhythmias

Sir:—The paper of Hosenpud *et al* (1986;56:55–61) showing the value of endomyocardial biopsy in patients with life threatening arrhythmias describes two cases of “granulomatous myocarditis”. The possibility that this was sarcoidosis is discussed but rather dismissed in favour of giant cell myocarditis.

Sarcoidosis of the heart does commonly present as life threatening arrhythmias and this diagnosis should be considered in any such case.¹ Of 300 cases in the United Kingdom that are known to me, 49 presented as sudden death, 24 subsequently died suddenly, 135 presented with serious ventricular arrhythmias or frequent ventricular extrasystoles, and 77 presented as complete heart block. The age of the onset of the heart block is considerably less than in cases of heart block from other causes.²

Clinical evidence of sarcoidosis may be quite inconspicuous and histological proof should be sought by biopsy of any promising organ or by Kveim biopsy.¹ When endomyocardial biopsy is positive it is diagnostic but when it is negative it is of no value.³

Diagnosis is important because steroids can be useful in the treatment of sarcoid heart disease. I

know of two severely affected patients in whom the successful use of steroids avoided transplantation. (M Billingham, personal communication).

Sarcoid heart disease continues to be diagnosed for the first time by the pathologist at necropsy or after transplantation in cases in which it has not even been considered. This suggests that many clinicians need to be reminded of this diagnosis.

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Notices

British Cardiac Society

The Annual General Meeting for 1987 will take place in Dundee on 8 and 9 April 1987, and the closing date for receipt of abstracts will be 6 January 1987.

The Autumn Meeting will be held at the Wembley Conference Centre, London, on 24 to 26 November 1987, and the closing date for receipt of abstracts will be 10 July 1987.

Cardiothoracic surgery

The 1st Scientific Session of the European Association for Cardiothoracic Surgery will take place in the Congress Center Hofburg in Vienna on 14 to 17 September 1987. Further details from Inter-convention, PO Box 80, A-1107 Vienna, Austria.

Validation of a study

An investigation by an ad hoc faculty committee of the University of California, San Diego, School of Medicine into the work of Dr Robert Slutsky has found evidence of research fraud in certain of his publications. The committee has placed the burden of proof on coauthors to establish the veracity of the experiments and methods reported in his other publications. The committee's examination of the paper

below and the testimony of coauthors did not result in concern about the validity of the publication:

John Watkins, Robert Slutsky, Julio Tubau, Joel Karliner. Scintigraphic study of relation between left ventricular peak systolic pressure and end-systolic volume in patients with coronary artery disease and normal subjects. *Br Heart J* 1982;48:39-47.

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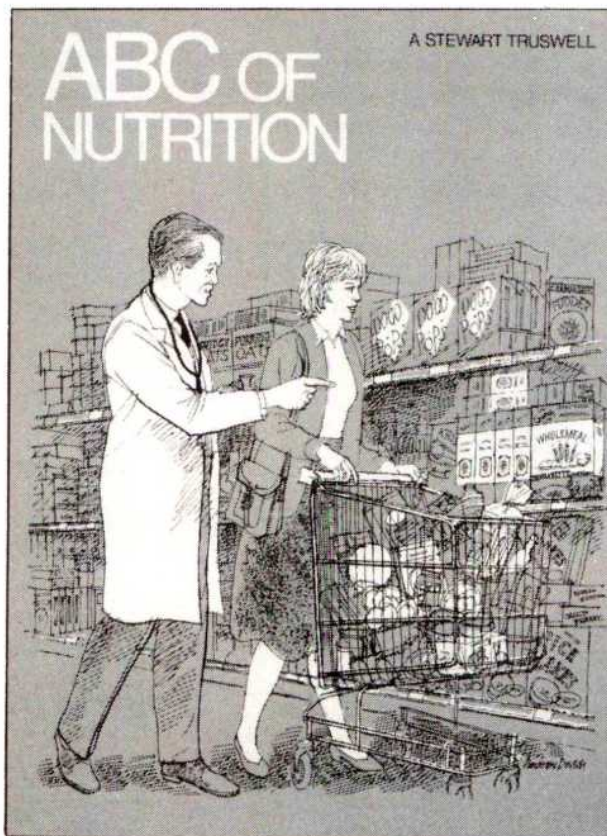
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AUTHOR INDEX

1986, Volume 56

- ADRIAN T E *see* Webb S C *et al*
 AITCHISON M *see* Behan W M H *et al*
 ALEXANDRE J-M *see* Funck-Brentano C *et al*
 ALEXOPOULOS D *see* Protonotarios N *et al*
 ANTONELLI D (& Shmilovitz L, Dharan M) Conjoined hearts: case report 486
 ARAKI H (& Hayata N, Matsuguchi T, Takeshita A, Nakamura M) Diagnosis of important fixed coronary stenosis in patients with variant angina by exercise tests after treatment with calcium antagonists 138
 ASHERSON R A (& Mackay I R, Harris E N) Myocardial infarction in a young man with systemic lupus erythematosus, deep vein thrombosis, and antibodies to phospholipid: case report 190
 ATKINSON L *see* Richardson P J *et al*
 BEEN M *see* De Bono D P *et al*
 BEHAN P O *see* Behan W M H *et al*
 BEHAN W M H (& Aitchison M, Behan P O) Pathogenesis of heart block in a fatal case of dermatomyositis: case report 479
 BENNETT D H Comparison of electrocardiographic and echocardiographic measures of left ventricular hypertrophy in the assessment of aortic stenosis: correspondence 105
 — *see also* Schofield P M *et al*
 BINI R M *see* McKay R *et al*
 BIOLLAZ J *see* Nicod P *et al*
 BLAND J M *see* D'Arbela P G *et al*
 BLOOM S R *see* Webb S C *et al*
 BOGAERT A M *see* De Scheerder I *et al*
 BONO D P DE *see* De Bono D P
 BOTT-SILVERMAN C *see* Proudfit W L *et al*
 BOVILL J G *see* Van Wezel H B *et al*
 BOWES R J *see* Schofield P M *et al*
 BRAAT S *see* Res J C J *et al*
 BRENTANO C FUNCK- *see* Funck-Brentano C
 BRESNAHAN J F *see* Sugrue D D *et al*
 BROOKS N *see* Schofield P M *et al*
 BROOKS N H *see* Schofield P M *et al*
 BROWN M J *see* Corr L *et al*
 BRUNNER H R *see* Nicod P *et al*
 BUCHANAN J D *see* Rogerson M B *et al*
 BUCKNALL C A (& Keeton B R, Curry P V L, Tynan M J, Sutherland G R, Holt D W) Intravenous and oral amiodarone for arrhythmias in children 278
 BULL C Interventional catheterisation in infants and children: editorial 197
 BURGESS J H *see* Daly P *et al*
 BURNS J E *see* Reid K G *et al*
 BUTLER M G *see* Kaye G C *et al*
 BUYZERE M DE *see* de Buyzere M
 CAMM A J *see* Kaye G C *et al*
 — Wiseman M N *et al*
 CHAPPELL M *see* Murray N *et al*
 CHARLES R G *see* Ramsdale D R *et al*
 CHARLESTON A J *see* Hangartner J R W *et al*
 CHATELLIER G *see* Funck-Brentano C *et al*
 CHATTERJEE K *see* Daly P *et al*
 CLEMENT D *see* De Scheerder I *et al*
 COBBE S M *see* Simpson I A *et al*
 COMMEAU Ph *see* Grollier G *et al*
 CORR L (& Grounds R M, Brown M J, Whitwam J G) Plasma catecholamine changes during cardiopulmonary bypass: a randomised double blind comparison of trimetaphan camsylate and sodium nitroprusside 89
 COULSHED N *see* Ramsdale D R *et al*
 COUPE M (& Dancy M, Pepper J) Coincidence of true and false left ventricular aneurysms after myocardial infarction: case report 567
 COUSINEAU D *see* Daly P *et al*
 CRAIG E *see* Smith D & Craige E
 CRAKE T *see* Quyyumi A A *et al*
 CREAM P A (Mathieson P W, Ruckards A F) Transluminal angioplasty of a stenosis of an internal mammary artery graft: case report 473
 CRICK J C P *see* Sowton E *et al*
 CURRY P V L *see* Bucknall C A *et al*
 D'ARBELA P G (& Silayan Z M, Bland J M) Comparability of M mode echocardiographic long axis and short axis left ventricular function derivatives 445
 D'ARDENNE A J *see* Kaye G C *et al*
 DALY P (& Rouleau J-L, Cousineau D, Burgess J H, Chatterjee K) Effects of captopril and a combination of hydralazine and isosorbide dinitrate on myocardial sympathetic tone in patients with severe congestive heart failure 152
 DANCY M Comparison of electrocardiographic and echocardiographic measures of left ventricular hypertrophy in the assessment of aortic stenosis: correspondence reply 105
 — *see also* Coupe M *et al*
 DAVID J *see* Nihoyannopoulos P *et al*
 DAVIES M J *see* Hangartner J R W *et al*
 DE BONO D P (& Lumley P, Been M, Keery R, Ince S E, Woodings D F) Effect of the specific thromboxane receptor blocking drug AH23848 in patients with angina pectoris 509
 DE BUYZERE M *see* De Scheerder I *et al*
 DE LANGE M *see* de Scheerder I *et al*
 DE SCHEERDER I (& De Buyzere M, Robbrecht J, De Lange M, Delanghe J, Bogaert A M, Clement D) Postoperative immunological response against contractile proteins after coronary bypass surgery 440
 DEL TORO S *see* Menahem S *et al*
 DELANGHE J *see* de Scheerder I *et al*
 DER STROOM J G VAN *see* Van der Stroom J G
 DETRANO R (& Yiannikas J, Sumpfendorfer C, Hobbs R E, Salcedo E E) Exercise digital subtraction ventriculography for the detection of ischaemic wall motion abnormalities in patients without myocardial infarction 131
 DEVERALL P *see* Sowton E *et al*
 DEWHURST N G *see* Rodrigues E A *et al*
 DHARAN M *see* Antonelli D *et al*
 DI SEGNI E (& Siegal A, Katzenstein M) Congenital diverticulum of the heart arising from the coronary sinus: case report 380
 DUNNING A J *see* Kan G *et al*
 DURRINGTON P N (& Hunt L, Ishola M, Kane J, Stephens W P) Serum apolipoproteins AI and B and lipoproteins in middle aged men with and without previous myocardial infarction 206
 EDMONDSON S J *see* Kaye G C *et al*
 EDWARDS A D (& Vickers M A, Morgan C J) Infective endocarditis affecting the eustachian valve: case report 561

- BENIGE M J *see* van Eenige M J
 EFTHIMIOU J *see* Quyyumi A A *et al*
 EPSTEIN E J *see* Ramsdale D R *et al*
 ERIKSSON P *see* Teien D *et al*
 EVANS D W (& Stovin P G I) Fatal heart block due to mesothelioma of the atrioventricular node: case report 572
 EVANS D WAINWRIGHT *see* Wainwright Evans D
 FIELDMAN A *see* Kiernan F J *et al*
 FIOLET J W T *see* Van Wezel H B *et al*
 FIRMIN D N *see* Underwood S R *et al*
 FITZGERALD E *see* Singh H *et al*
 FLEMING H A Unexpected myocardial disease in patients with life threatening arrhythmias. correspondence 575
 FOALE R (& Nihoyannopoulos P, McKenna W, Kleinbenné A, Nadazdin A, Rowland E, Smith G) Echocardiographic measurement of the normal adult right ventricle 33
 — Ribeiro P, McKenna W J, Oakley C M, Driskler D M, Rowland E) Right ventricular abnormalities in ventricular tachycardia of right ventricular origin. relation to electrophysiological abnormalities 45
 FORMAN M B *see* Kopelman H A *et al*
 FOX K M (& Krikler D M) Early treatment of unstable angina editorial 398
 — *see also* Levy R D *et al*
 Quyyumi A A *et al*
 Underwood S R *et al*
 FRIEDLI B *see* Meier B *et al*
 FUJIWARA H *see* Tanaka M *et al*
 FUNCK-BRENTANO C (& Chatellier G, Alexandre J-M) Reversible renal failure after combined treatment with enalapril and frusemide in a patient with congestive heart failure. correspondence reply 489
 FYFE T (& Robinson J F) Failure of Quintech Tx pacemaker caused by loss of stimulus-T interval shortening during exercise. case report 391
 GATHI D *see* Sanderson J E *et al*
 GEDDES J S Twenty years of prehospital coronary care. editorial 491
 GENEST J The atrial natriuretic factor 302
 GEZERLIS P *see* Protonotarios N *et al*
 GIBBS J L (& Qureshi S A, Grieve L, Webb C, Radley Smith R, Yacoub M H) Doppler echocardiography after anatomical correction of transposition of the great arteries 67
 GIBSON D (& Mehmel H, Schwarz F, Li K, Kubler W) Changes in left ventricular regional asynchrony after intracoronary thrombolysis in patients with impending myocardial infarction 121
 GIBSON D G *see* Hammermeister K E *et al*
 GILES M S *see* Wiseman M N *et al*
 GODMAN M J *see* Reid K G *et al*
 GOH T H *see* Menahem S *et al*
 GOORMASTIC M *see* Proudfit W L *et al*
 GOWERS J *see* Shaw D B *et al*
 GOY J J *see* Nicod P *et al*
 GRAHAM B S *see* Kopelman H A *et al*
 GREEN G J *see* Ramsdale D R *et al*
 GRIEVE L *see* Gibbs J L *et al*
 GRIFFIN B *see* Sowton E *et al*
 GROLLIER G (& Commeau Ph, Potier J C) Angioplasty of an occluded left anterior descending coronary artery: usefulness of retrograde opacification of the distal part of the occluded vessel via the contralateral coronary artery in positioning the balloon catheter. case report 377
 GROUNDS R M *see* Corr L *et al*
 GUERON M *see* Weinhouse E *et al*
 GUSSARSKY Y *see* Weinhouse E *et al*
 HACKETT D *see* Nihoyannopoulos P *et al*
 HACKWORTHY R A (& Vogel M B, Harris P J) Influence of infarct artery patency on the relation between initial ST segment elevation and final infarct size 222
 HALLIDIE-SMITH K A *see* Morais P *et al*
 HAMMERMEISTER K E (& Gibson D G, Hughes D) Regional variation in the timing and extent of left ventricular wall motion in normal subjects 226
 HAMMES L N *see* Sugrue D D *et al*
 HANGARTNER J R W (& Charleston A J, Davies M J, Thomas A C) Morphological characteristics of clinically significant coronary artery stenosis in stable angina 501
 HANNAN W J *see* Rodrigues E A *et al*
 HARRIS E N *see* Asherson R A *et al*
 HARRIS P J *see* Hackworthy R A *et al*
 HAYATE N *see* Araki H *et al*
 HEIKKILA J *see* Huikuri H V *et al*
 HENDERSON A H *see* Lewis M J & Henderson A H
 HENDRY W G *see* Webb S C *et al*
 HERBINGER W *see* Leisch F *et al*
 HOBBS R E *see* Detrano R *et al*
 HOFBAUER K G *see* Nicod P *et al*
 HOLLAND INTERUNIVERSITY NIFEDIPINE/METOPROLOL TRIAL (HINT) RESEARCH GROUP Early treatment of unstable angina in the coronary care unit: a randomised, double blind, placebo controlled comparison of recurrent ischaemia in patients treated with nifedipine or metoprolol or both 400
 HOLMES D R *see* Sugrue D D *et al*
 HOLT D W *see* Bucknall C A *et al*
 HOSENPUD J D (& McAnulty J H, Niles N R) Unexpected myocardial disease in patients with life threatening arrhythmias 55
 HOUSTON A B *see* Simpson I A *et al*
 HUGHES D *see* Hammermeister K E *et al*
 HUIKURI H V (& Korhonen U R, Heikkilä J, Takkunen J T) Detection of coronary artery disease by thallium scintigraphy in patients with valvular heart disease 146
 HUMPHRIES S E Familial hypercholesterolaemia as an example of early diagnosis of coronary artery disease risk by DNA techniques. editorial 201
 HUNT L *see* Durrington P N *et al*
 HUTTON I *see* Simpson I A *et al*
 IIDA K *see* Matsuda M *et al*
 INCE S E *see* De Bono D P *et al*
 INGRAM A *see* Kenny R A *et al*
 ISHIKAWA K *see* Ishikawa M & Ishikawa K
 ISHIKAWA M (& Ishikawa K) Influence of profuse sweating on systolic time intervals 176
 ISHOLA M *see* Durrington P N *et al*
 ITO I *see* Matsuda M *et al*
 JENKINS B S *see* Wilmshurst P T *et al*
 JEWITT D E *see* Richardson P J *et al*
 JOHNS J A *see* Menahem S *et al*
 JOY M *see* Stewart JT *et al*
 JUUL S M *see* Wilmshurst P T *et al*
 KAN G (& Visser C A, Koolen J J, Dunning A J) Short and long term predictive value of admission wall motion score in acute myocardial infarction. a cross sectional echocardiographic study of 345 patients 422
 KANE J *see* Durrington P N *et al*
 KARLINER J *see* Watkins J *et al*
 KARP K *see* Teien D *et al*
 KATZENSTEIN M *see* Di Segni E *et al*
 KAWAI C *see* Tanaka M *et al*
 KAYE G C (& Butler M G, d'Ardenne A J, Edmondson S J, Camm A J, Slavin G) Isolated atrial amyloid contains atrial natriuretic peptide. a report of six cases 317
 KEERY R *see* De Bono D P *et al*
 KEETON B R *see* Bucknall C A *et al*
 KEKWICK C A *see* Shaw D B *et al*
 KENNY R A (& Ingram A, Mitsuoka T, Walsh K, Sutton R) Optimum pacing mode for patients with angina pectoris 463

- KERSCHNER K *see* Leisch F *et al*
 KIERNAN F J (& Kluger J, Regnier J C, Rutkowski M, Fieldman A)
 Epoprostenol sodium (prostacyclin) infusion in acute myocardial
 infarction 428
 KLEINERENNE A *see* Foale R *et al*
 KLIPSTEIN R H *see* Underwood S R *et al*
 KLUGER J *see* Kiernan F J *et al*
 KNAPP M F *see* Linden R J & Knapp M F
 KOIWAYA Y *see* Nakagawa S *et al*
 KOOLEN J J *see* Kan G *et al*
 Van Wezel HB *et al*
 KOPELMAN H A (& Graham B S, Forman M B) Myocardial abscess
 with complete heart block complicating anaerobic infective
 endocarditis case report 101
 KORHONEN U R *see* Hukuri H V *et al*
 KRAMER J R *see* Proudfoot W L *et al*
 KRIKLER D M *see* Foale R A *et al*
 Fox K M & Krikler D M
 Webb S C *et al*
 KUBLER W *see* Gibson D *et al*
 KUWAKO K *see* Matsuda M *et al*
- LANE G E *see* Sugrue D D *et al*
 LANGE M DE *see* de Lange M
 LAU K C *see* Leung M P *et al*
 LEISCH F (& Schutzenberger W, Kerschner K, Herbringer W)
 Influence of a variant angina on the results of percutaneous
 transluminal coronary angioplasty 341
 LEUNG M P (& Mok C K, Lau K C, Lo R, Yeung C Y) The role
 of cross sectional echocardiography and pulsed Doppler ultra-
 sound in the management of neonates in whom congenital heart
 disease is suspected. A prospective study 73
 LEVY R D (& Shapiro L M, Wright C, Mockus L, Fox K M)
 Haemodynamic response to myocardial ischaemia during
 unrestricted activity, exercise testing, and atrial pacing assessed
 by ambulatory pulmonary artery pressure monitoring 12
 ———— Syndrome X: the haemodynamic significance of ST
 segment depression 353
 ———— The haemodynamic response to myocardial ischaemia
 in ambulant patients with variant angina 518
 ———— The haemodynamic significance of asymptomatic ST
 segment depression assessed by ambulatory pulmonary artery
 pressure monitoring 526
 LEWIS M J (& Henderson A H) Abrupt withdrawal of atenolol in
 patients with severe angina: comparison with the effects of treat-
 ment: correspondence 195
 LI K *see* Gibson D *et al*
 Lincoln C *et al*
 LINCOLN C (& Redington A N, Li K, Mattos S, Shinebourne E A,
 Rigby M L) Anatomical correction for complete transposition
 and double outlet right ventricle: intermediate assessment of
 functional results 259
 LINDEN R J (& Knapp M F) Is atrial natriuretic peptide really a
 hormone?: editorial 299
 LO R *see* Leung M P *et al*
 LONGMORE D B *see* Underwood S R *et al*
 LOVETT D *see* Stewart J T *et al*
 LUMLEY P *see* De Bono D P *et al*
 LYONS J *see* Murray N *et al*
- McANULTY J H *see* Hosenpud J D *et al*
 MCCREDIE R M *see* McKenzie W B *et al*
 MCGILCHRIST C A *see* McKenzie W B *et al*
 MACKAY I R *see* Asherson R A *et al*
 MCKAY R (& Bini R M, Wright J P) Staged septation of double inlet
 left ventricle case report 563
 MCKENNA W *see* Foale R A *et al*
 MCKENNA W J *see* Foale R A *et al*
- McKENZIE W B (& McCredie R M, McGilchrist C A, Wilcken D
 E L) Smoking: a major predictor of left ventricular function after
 occlusion of the left anterior descending coronary artery 496
 MACKINTOSH A F *see* Tseu F L *et al*
 McMURRAY J (& Matthews D M) Reversible renal failure after
 combined treatment with enalapril and frusemide in a patient
 with congestive heart failure: correspondence 489
 MATHIESEN P W *see* Crean P A *et al*
 MATSUDA M (& Sekiguchi T, Sugishita Y, Kuwako K, Iida K, Ito
 I) Reliability of non-invasive estimates of pulmonary hyper-
 tension by pulsed Doppler echocardiography 158
 MATSUGUCHI T *see* Araki H *et al*
 MATTHEWS D M *see* McMurray J & Matthews D M
 MATTOS S *see* Lincoln C *et al*
 MEHMERL H *see* Gibson D *et al*
 MEIER B (& Friedli B, Oberhansli I) Trefol balloon for aortic
 valvuloplasty: case report 292
 MEIJLER F L The pulse in atrial fibrillation: editorial 1
 MENAHEM S (& Johns J A, Del Torso S, Goh T H, Venables A W)
 Evaluation of aortic valve prolapse in ventricular septal defect 242
 MITSUOKA T *see* Kenny R A *et al*
 MOCKUS L *see* Levy R D *et al*
 MOCKUS L J *see* Levy R D *et al*
 Quyyum A A *et al*
 MOK C K *see* Leung M P *et al*
 MORAIS P (& Westaby S, Hallidie-Smith K A) Left ventricular
 outflow tract obstruction due to anomalous mitral valve: success-
 ful mitral valve replacement in a four month old infant. case
 report 385
 MORGAN C J *see* Edwards A D *et al*
 MORGANS C M *see* Rogerson M E *et al*
 MORLEY C A *see* Tseu F L *et al*
 MUIR A L *see* Rodrigues E A *et al*
 MURRAY N (& Lyons J, Chappell M) Crescentic glomerulo-
 nephritis: a possible complication of streptokinase treatment for
 myocardial infarction: case report 483
- NADAZDIN A *see* Foale R *et al*
 NAKAGAWA S (& Yamamoto Y, Koiwaya Y) Alpha receptors and
 ventricular tachycardia after clonidine withdrawal. correspon-
 dence 194
 NAKAMURA M *see* Araki H *et al*
 NICOD P (& Biollaz J, Waechter B, Goy J J, Polikar R, Schlapfer J,
 Schaller M D, Turini G A, Nussberger J, Hofbauer K G,
 Brunner H R) Hormonal, global, and regional haemodynamic
 responses to a vascular antagonist of vasopressin in patients with
 congestive heart failure with and without hyponatraemia 433
 NIHOYANNOPOULOS P (& Venkatesan P, David J, Hackett D,
 Valentine H, Oakley C M) Left atrial myxoma: new perspectives
 in the diagnosis of murmur free cases 554
 ———— *see* Foale R *et al*
 Foale R A *et al*
 NILES N R *see* Hosenpud J D *et al*
 NUSSBERGER J *see* Nicod P *et al*
- OAKLEY C M *see* Foale R A *et al*
 Nihoyannopoulos P *et al*
 OBERHANSLI I *see* Meier B *et al*
 OLSEN E G J *see* Sanderson J E *et al*
 ORTIZ E (& Somerville J) Assessment by cross sectional echo-
 cardiography of surgical "mitral valve" disease in children and
 adolescents 267
- PAPOUCHADO M (& Pitcher D W) Ventricular pacing improves
 exercise tolerance in patients with chronic heart block 366
 PATEL P N *see* Watson R D S & Patel P N
 PATRICK M R *see* Van Wezel H B *et al*
 PATSOURAKOS P *see* Protonotarios N *et al*
 PEPLOR M M WEBB *see* Webb-Peploe M M

- PEPPER J *see* Coupe M *et al*
 PERRINS E J *see* Quyyumi A A *et al*
 PIEHLER J M *see* Sugrue D D *et al*
 PITCHER D W *see* Papouchado M & Pitcher D W
 POLIKAR R *see* Nicod P *et al*
 POOLE-WILSON P A *see* Underwood S R *et al*
 POTIER J C *see* Grolhier G *et al*
 PROTONOTARIOS N (& Tsatsopoulou A, Patsourakos P, Alexopoulos D, Gezerlis P, Simitsis S, Scampardoni G) Cardiac abnormalities in familial palmoplantar keratosis 321
 PROUDFIT W L John Hunter on heart disease. review 109
 —(& Kramer J R, Bott-Silverman C, Goormastic M) Survival of non-surgical patients with mild angina or myocardial infarction without angina 213
 QURESHI S A *see* Gibbs J L *et al*
 QUYYUMI A A (& Crake T, Mockus L J, Wright C A, Rickards A F, Fox K M) Value of the bipolar lead CM5 in electrocardiography 372
 —(& Efthimiou J, Quyyumi A, Mockus L J, Spiro S G, Fox K M) Nocturnal angina: precipitating factors in patients with coronary artery disease and those with variant angina 346
 —(& Raphael M, Perrins E J, Shapiro L M, Rickards A F, Fox K M) Incidence of spasm at the site of previous successful transluminal coronary angioplasty: effect of ergometrine maleate in consecutive patients 27
 —*see also* Quyyumi A A *et al*
 RADLEY SMITH R *see* Gibbs J L *et al*
 RAJ M V J *see* Wainwright Evans D and Raj M V J
 RAO P S Transcatheter treatment of pulmonary stenosis and coarctation of the aorta. experience with percutaneous balloon dilatation 250
 RAPHAEL M *see* Quyyumi A A *et al*
 RAMSDALE D R (& Epstein E J, Coulshed N) Constructive pericarditis after myocardial infarction: case report 476
 —(& Green G J, Charles R G) Abnormal diastolic movement of the interventricular septum caused by a prolapsing right atrial myxoma: case report 569
 RAWLES J M (& Rowland E) Is the pulse in atrial fibrillation irregularly irregular? 4
 REDINGTON A N *see* Lincoln C *et al*
 REECE I J *see* Simpson I A *et al*
 REEDER G S *see* Sugrue D D *et al*
 REEDER R S O *see* Underwood S R *et al*
 REGNIER J C *see* Kiernan F J *et al*
 RED K G (& Godman M J, Burns J E) Truncus arteriosus successful surgical correction without the use of a valved conduit case report 388
 REMME W J *see* Res J C J *et al*
 RES J C J (& Simoons M L, van der Wall E B, van Eenige M J, Vermeer F, Verheugt F W A, Wijns W, Braat S, Remme W J, Serruys P W, Roos J P) Long term improvement in global left ventricular function after early thrombolytic treatment in acute myocardial infarction report of a randomised multicentre trial of intracoronary streptokinase in acute myocardial infarction 414
 RIBEIRO P *see* Foale R A *et al*
 RICHARDSON P J (& Wodak A D, Atkinson L, Saunders J B, Jewitt D E) Relation between alcohol intake, myocardial enzyme activity, and myocardial function in dilated cardiomyopathy: evidence for the concept of alcohol induced heart muscle disease 165
 RICKARDS A F (& Somerville J) Successful balloon aortic valvotomy in a child with a pulmonary hypertensive duct and aortic valve stenosis: case report 185
 —*see* Crean P A *et al*
 Quyyumi A A *et al*
 RIGBY M L *see* Lincoln C *et al*
 ROBBRECHT J *see* de Scheerder I *et al*
 ROBERTS K D *see* Sibley Y D L *et al*
 ROBINSON J F *see* Fyfe T & Robinson J F
 RODRIGUES E A (& Dewhurst N G, Smart L M, Hannan W J, Muir A L) Diagnosis and prognosis of right ventricular infarction 19
 ROGERSON M B (& Buchanan J D, Morgans C M) Left atrial rupture in osteogenesis imperfecta: case report 187
 ROOS J P *see* Res J C J *et al*
 ROULEAU J-L *see* Daly P *et al*
 ROWLAND E *see* Foale R A *et al*
 Foale R A *et al*
 Rawles J M & Rowland E
 RUTKOWSKI M *see* Kiernan F J *et al*
 RUTTLEY M S T *see* Singh H *et al*
 Singh H & Ruttley M S T
 SALCEDO E E *see* Detrano R *et al*
 SAUNDERS J B *see* Richardson P J *et al*
 SANDERSON J E (& Olsen E G J, Gates D) Peripartum heart disease: an endomyocardial biopsy study 285
 SAVAGE P E *see* Underwood S R *et al*
 SCAMPARDONI G *see* Protonotarios N *et al*
 SCHALLER M D *see* Nicod P *et al*
 SCHEERDER I De *see* De Scheerder I
 SCHLAPPER J *see* Nicod P *et al*
 SCHOFIELD P M (& Brooks N H, Bennett D H) Left ventricular dysfunction in patients with angina pectoris and normal coronary angiograms 327
 —(& Bowes R J, Brooks N, Bennett D H) Exercise capacity and spontaneous heart rhythm after transvenous fulguration of atrio-ventricular conduction 358
 SCHUTZENBERGER W *see* Leisch F *et al*
 SCHWARZ F *see* Gibson D *et al*
 SEGNI E Di *see* Di Segni E
 SEKIGUCHI T *see* Matsuda M *et al*
 SERRUYS P W *see* Res J C J *et al*
 SHAPIRO L M *see* Levy R D *et al*
 Quyyumi A A *et al*
 SHAW D B (& Kekwick C A, Veale D, Gowers J, Whistance T) Survival in second degree atrioventricular block: correspondence reply 107
 SHINEBOURNE E A *see* Lincoln C *et al*
 SEMILOVITZ L *see* Antonelli D *et al*
 SIBLEY Y D L (& Roberts K D, Silove E D) Surgical correction of anomalous origin of right pulmonary artery from aorta in a four day old neonate. case report 98
 SIEGAL A *see* Di Segni E *et al*
 SILAYAN Z M *see* D'Arbela P G *et al*
 SILOVE E D *see* Sibley Y D L *et al*
 SILVERMAN C BOTT- *see* Bott-Silverman C
 SIMITSIS S *see* Protonotarios N *et al*
 SIMOONS M L *see* Res J C J *et al*
 SIMPFENDORFER C *see* Detrano R *et al*
 SIMPSON I A (& Reece I J, Hourston A B, Hutton I, Wheatley D J, Cobbe S M) Non-invasive assessment by Doppler ultrasound of 155 patients with bioprosthetic valves: a comparison of the Westex porcine, low profile Ionescu-Shiley, and Hancock pericardial bioprostheses 83
 SINGH H (& Fitzgerald E, Ruttley M S T) Computed tomography: the investigation of choice for aortic dissection 171
 —(& Ruttley M S T) Intracoronary thrombolytic treatment: another hazard: case report 182
 SLAVIN G *see* Kaye G C *et al*
 SLUTSKY R Validation of work 576
 —*see also* Watkins J *et al*
 SMART L M *see* Rodrigues E A *et al*
 SMITH D (& Craig E) Mechanism of the dicrotic pulse 531
 SMITH G *see* Foale R *et al*
 SMITH H C *see* Sugrue D D *et al*
 SMITH K A HALLIDIE- *see* Hallidie-Smith K A
 SMITH R RADLEY *see* Radley Smith R
 SOFER S *see* Weinhouse E *et al*

- SOMERVILLE J Congenital heart disease in adults and adolescents: editorial 395
— *see also* Ortiz E & Somerville J
 Richards A F & Somerville J
 Warnes C A & Somerville J
- SOWTON E (& Timmus A D, Crick J C P, Griffin B, Yates A K, Deverall P) Early results after percutaneous transluminal coronary angioplasty in 400 patients 115
- SPIRO S G *see* Quyyumi A A *et al*
- STEPHENS W P *see* Durrington P N *et al*
- STEWART J T (& Lovett D, Joy M) Reversible renal failure after combined treatment with enalapril and frusemide in a patient with congestive heart failure: correspondence 489
- STOVIN P G I *see* Evans D W & Stovin P G I
- STROOM J G VAN DER *see* Van der Stroom J G
- SUGISHITA Y *see* Matsuda M *et al*
- SUGRUE D D (& Holmes D R, Smith H C, Reeder G S, Lane G E, Vlietstra R E, Bresnahan J F, Hammes L N, Piehler J M) Coronary artery thrombus as a risk factor for acute vessel occlusion during percutaneous transluminal coronary angioplasty, improving results 62
- SUTHERLAND G R *see* Bucknall C A *et al*
- SUTTON R *see* Kenny R A *et al*
- TAKESHITA A *see* Araki H *et al*
- TAKKUNEN J T *see* Huikuri H V *et al*
- TANAKA M (& Fujiwara H, Kawai C) Pathological features of hypertrophic cardiomyopathy without asymmetrical septal hypertrophy: case report 294
- TEEN D (& Karp K, Eriksson P) Non-invasive estimation of the mean pressure difference in aortic stenosis by Doppler ultrasound 450
- THOMAS A C *see* Hangartner J R W *et al*
- THOMPSON D S *see* Wilmsworth P T *et al*
- TIMMIS A D *see* Sowton E *et al*
- TORSO S DEL *see* Del Torsio S
- TSATSPOPOULOU A *see* Protonotarios N *et al*
- TSEU F L (& Morley C A, Mackintosh A F) Oral xamoterol in patients with sinusoidal disease 469
- TUBAU J *see* Watkins J *et al*
- TURINI G A *see* Nicod P *et al*
- TYNAN M J *see* Bucknall C A *et al*
- UNDERWOOD S R (& Klipstein R H, Firmin D N, Fox K M, Poole-Wilson P A, Rees R S O, Longmore D B) Magnetic resonance assessment of aortic and mitral regurgitation 455
— (& Rees R S O, Savage P E, Klipstein R H, Firmin D N, Fox K M, Poole-Wilson P A, Longmore D B) Assessment of regional left ventricular function by magnetic resonance 334
- VALANTINE H *see* Nihoyannopoulos P *et al*
- VAN EENIGE M J *see* Res J C J *et al*
- VAN DER STROOM J G *see* Van Wezel H B *et al*
- VAN DER WALL E *see* Res J C J *et al*
- VAN WEZEL H B (& Bovill J G, Koolen J J, Patrick M R, Fiolet J W T, Van der Stroom J G) Influence of glyceryl trinitrate and nifedipine on coronary sinus blood flow and global myocardial metabolism during coronary artery operation 272
- VIALE D *see* Shaw D B *et al*
- VENABLES A W *see* Menahem S *et al*
- VENKATESAN P *see* Nihoyannopoulos P *et al*
- VERHEUGT F W A *see* Res J C J *et al*
- VERMEER F *see* Res J C J *et al*
- VICKERS M A *see* Edwards A D *et al*
- VISSER C A *see* Kan G *et al*
- VLIETSTRA R E *see* Sugrue D D *et al*
- VOGAL M B *see* Hackworthy R A *et al*
- WAEBER B *see* Nicod P *et al*
- WAINWRIGHT EVANS D (& Raj M V J) Comparison of electrocardiographic and echocardiographic measures of left ventricular hypertrophy in the assessment of aortic stenosis: correspondence 105
- WALKER P R Abrupt withdrawal of atenolol in patients with severe angina: comparison with the effects of treatment: correspondence reply 195
- WALL E B VAN DER *see* van der Wall E B
- WALSH K *see* Kenny R A *et al*
- WANDERMAN K L *see* Weinhouse E *et al*
- WARNES C A (& Somerville J) Tricuspid atresia in adolescents and adults: current state and late complications 535
- WATKINS J (& Slutsky R, Tubau J, Karlmer J) Scintigraphic study of relation between left ventricular peak systolic pressure and end-systolic volume in patients with coronary artery disease and normal subjects *Br Heart J* 1982;48:39-47 (Validation of Slutsky's work) 576
- WATSON R D S (& Patel P N) Survival in second degree atrio-ventricular block: correspondence 107
- WEBB C *see* Gibbs J L *et al*
- WEBB-PEPLOS M M *see* Wilmsworth P T *et al*
- WEBB S C (& Krikler D M, Hendry W G, Adrian T E, Bloom S R) Electrophysiological actions of somatostatin on the atrio-ventricular junction in sinus rhythm and reentry tachycardia 236
- WEINHOUSE E (& Wanderman K L, Sofer S, Gussarsky Y, Gueron M) Viral myocarditis simulating dilated cardiomyopathy in early childhood: evaluation by serial echocardiography 94
- WESTABY S *see* Morris P *et al*
- WEZEL H B VAN *see* Van Wezel H B
- WHEATLEY D J *see* Simpson I A *et al*
- WHISTANCE T *see* Shaw D B *et al*
- WHITWAM J G *see* Corr L *et al*
- WIJNS W *see* Res J C J *et al*
- WILCKEN D E L *see* McKenzie W B *et al*
- WILDE P Radiation hazards for cardiologists: correspondence 394
- WILMSWORTH P T (& Thompson D S, Juul S M, Jenkins B S, Webb-Peplos M M) Effects of verapamil on haemodynamic function and myocardial metabolism in patients with hypertrophic cardiomyopathy 544
- WILSON P A POOLE- *see* Poole-Wilson P A
- WISEMAN M N (& Giles M S, Camm A J) Unusual echocardiographic appearance of intracardiac thrombi in a patient with endomyocardial fibrosis: case report 179
- WODAK A D *see* Richardson P J *et al*
- WOODINGS D F *see* De Bono D P *et al*
- WRIGHT C *see* Levy R D *et al*
- WRIGHT C A *see* Quyyumi A A *et al*
- WRIGHT J P *see* McKay R *et al*
- YACOB M H *see* Gibbs J L *et al*
- YAMAMOTO Y *see* Nakagawa S *et al*
- YATES A K *see* Sowton E *et al*
- YEUNG C Y *see* Leung M P *et al*
- YIANNIKAS J *see* Detrano R *et al*

SUBJECT INDEX

1986, Volume 56

- AH23848, effect in angina pectoris (De Bono *et al*) 509
- Alcohol intake, myocardial enzyme activity, and myocardial function, in dilated cardiomyopathy, relation between (Richardson *et al*) 165
- Alpha receptors and ventricular tachycardia, after clonidine withdrawal: correspondence (Nakagawa *et al*) 194
- Ambulatory pulmonary artery pressure monitoring
assessing asymptomatic ST segment depression, haemodynamic significance (Levy *et al*) 526
in myocardial ischaemia with variant angina (Levy *et al*) 518
value of bipolar lead CM5 (Quyyumi *et al*) 372
- Amiodarone, intravenous and oral, for arrhythmias, children (Bucknall *et al*) 278
- Angina pectoris
mild, survival of non-surgical patients (Proudfit *et al*) 213
and normal coronary angiograms, left ventricular dysfunction (Schofield *et al*) 327
effect of specific thromboxane receptor blocking drug AH23848 (De Bono *et al*) 509
nocturnal, precipitating factors in coronary artery disease and variant angina (Quyyumi *et al*) 346
optimum pacing mode (Kenny *et al*) 463
severe, abrupt withdrawal of atenolol, comparison with effects of treatment: correspondence (Lewis & Henderson: Walker) 195
stable, morphological characteristics of clinically significant coronary artery stenosis (Hangartner *et al*) 501
unstable, early treatment: editorial (Fox & Krikler) 398
early treatment in coronary care unit, HINT Research Group 400
variant, diagnosis of important fixed coronary stenosis by exercise tests after treatment with calcium antagonists (Araki *et al*) 138
influence on results of percutaneous transluminal coronary angioplasty (Leisch *et al*) 341
and myocardial ischaemia, ambulatory pulmonary artery pressure monitoring (Levy *et al*) 518
precipitating factors of nocturnal angina (Quyyumi *et al*) 346
- Angioplasty *see also* Balloon: Percutaneous: Valvuloplasty
- Antibodies to phospholipid, and deep vein thrombosis, in systemic lupus erythematosus, and myocardial infarction: case report (Asherson *et al*) 190
- Aorta (aortic)
dissection, computed tomography as investigation of choice (Singh *et al*) 171
regurgitation, magnetic resonance assessment (Underwood *et al*) 455
valve, prolapse, evaluation in ventricular septal defect (Menahem *et al*) 242
stenosis assessment, electrocardiographic and echocardiographic measures of left ventricular hypertrophy compared: correspondence (Bennett: Wainwright Evans & Raj: Dancy) 105
mean pressure difference, non-invasive estimation by Doppler ultrasound (Teien *et al*) 450
and pulmonary hypertensive duct, successful balloon aortic valvotomy: case report (Rickards & Somerville) 185
- Apolipoproteins AI and B serum, and lipoproteins, and ischaemic heart disease (Durrington *et al*) 206
- Arrhythmias
children, treatment with intravenous and oral amiodarone (Bucknall *et al*) 278
life threatening, and sarcoid heart disease: correspondence (Fleming) 575
- Atenolol, abrupt withdrawal, in severe angina, comparison with effects of treatment: correspondence (Lewis & Henderson: Walker) 195
- Atrial
amyloid, isolated, contains atrial natriuretic peptide, report of 6 cases (Kaye *et al*) 317
fibrillation, pulse in, irregularly irregular (Rawles & Rowland). 4
pulse in: editorial (Meijler). 1
natriuretic peptide, containing isolated atrial amyloid, report of 6 cases (Kaye *et al*) 317
is this really a hormone. editorial (Linden & Knapp). 299
research review and historical account (Genest) 302
pacing, in myocardial ischaemia, haemodynamic response to pulmonary artery pressure monitoring (Levy *et al*) 12
rupture, left in osteogenesis imperfecta: case report (Rogerson *et al*) 187
- Atroventricular block, second degree, survival. correspondence (Watson & Patel: Shaw *et al*) 107
- Balloon
aortic valvotomy, successful, in pulmonary hypertensive duct and aortic valve stenosis: case report (Rickards & Somerville). 185
dilatation of pulmonary stenosis and coarctation of the aorta (Rao) 250
techniques, infants and children: editorial (Bull) 197
trefoil, for aortic valvuloplasty: case report (Meier *et al*) 292
Bipolar lead CM5 in electrocardiography, value (Quyyumi *et al*) 372
- Blood flow, coronary sinus, and global myocardial metabolism, influence of glyceryl trinitrate and nifedipine, during coronary artery operation (van Wezel *et al*) 272
- Calcium antagonists, and exercise testing, in detection of coronary stenosis in variant angina (Areki *et al*) 138
- Captopril, and hydralazine and isosorbide dinitrate, effects on myocardial sympathetic tone in severe congestive heart failure (Daly *et al*) 152
- Cardiomyopathy, dilated, early childhood, evaluation by serial echocardiography (Weinhouse *et al*) 94
- Cardiomyopathy, dilated, relation between alcohol intake, myocardial enzyme activity, and myocardial function (Richardson *et al*) 165
- Cardiopulmonary bypass, plasma catecholamine changes during, trimetaphan camsylate and sodium nitroprusside compared (Cort *et al*) 89
- Catecholamine, plasma, changes during cardiopulmonary bypass, trimetaphan camsylate and sodium nitroprusside compared (Cort *et al*) 89
- Catheterisation, interventional, infants and children. editorial (Bull). 197
- Clonidine withdrawal, α receptors and ventricular tachycardia after: correspondence (Nakagawa *et al*) 194
- Coarctation of the aorta, balloon dilatation (Rao) 250
- Computed tomography, for aortic dissection, investigation of choice (Singh *et al*) 171
- Congenital heart disease
adults and adolescents: editorial (Somerville). 395
echocardiography, neonates (Leung *et al*) 73
- Congestive heart failure
reversible renal failure after combined treatment with enalapril and frusemide: correspondence (Stewart *et al*: McMurray & Matthews: Funck-Bretano *et al*) 489
vasopressin antagonist, hormonal, global, and regional haemodynamic responses (Nicod *et al*) 433
- Conjoined hearts: case report (Antonelli *et al*) 486
- Coronary
artery disease, detection by thallium scintigraphy in valvar heart disease (Huikuri *et al*) 146

- early diagnosis of risk, familial hypercholesterolaemia, DNA techniques: editorial (Humphries). 201
- precipitating factors of nocturnal angina (Quyyumi *et al*). 346
- occluded left anterior descending, percutaneous transluminal coronary angioplasty: case report (Grollier *et al*). 377
- stenosis, clinically significant, in stable angina, morphological characteristics (Hangartner *et al*). 501
- detection in variant angina, exercise testing (Araki *et al*). 138
- thrombus, as risk factor for acute vessel occlusion during percutaneous transluminal coronary angioplasty (Sugrue *et al*). 62
- bypass surgery, postoperative immunological response against contractile proteins (de Scheerder *et al*). 440
- care, prehospital, twenty years: editorial (Geddes). 491
- Correction 298
- Correspondence
- Abrupt withdrawal of atenolol in patients with severe angina: comparison with the effects of treatment (Lewis & Henderson: Walker). 195
- α receptors and ventricular tachycardia after clonidine withdrawal (Nakagawa *et al*). 194
- Comparison of electrocardiographic and echocardiographic measures of left ventricular hypertrophy in the assessment of aortic stenosis (Bennett, Wainwright Evans & Raj: Dancy). 105
- Radiation hazards for cardiologists (Wilde). 394
- Reversible renal failure after combined treatment with enalapril and frusemide in a patient with congestive heart failure (Stewart *et al*: McMurray & Matthews: Funck-Brentano *et al*). 489
- Survival in second degree atrioventricular block (Watson & Patel: Shaw *et al*). 107
- Unexpected myocardial disease in patients with life threatening arrhythmias (Fleming). 575
- Crescentic glomerulonephritis, possible complication of streptokinase treatment for myocardial infarction: case report (Murray *et al*). 483
- Cross sectional echocardiography and pulsed Doppler ultrasound, in congenital heart disease in neonates (Leung *et al*). 73
- DDD pacing mode, in angina pectoris (Kenny *et al*). 463
- Deep vein thrombosis, and antibodies to phospholipid, in systemic lupus erythematosus, and myocardial infarction: case report (Asherson *et al*). 190
- Dermatomyositis, fatal, pathogenesis of heart block: case report (Behan *et al*). 479
- Dicrotic pulse, mechanism (Smith & Craig). 531
- Digital subtraction angiography, ischaemic wall motion abnormalities without myocardial infarction (Detrano *et al*). 131
- Diverticulum of the heart, congenital, arising from the coronary sinus: case report (Di Segni *et al*). 380
- DNA techniques, familial hypercholesterolaemia as example of early diagnosis of coronary artery disease risk: editorial (Humphries). 201
- Doppler echocardiography
- after anatomical correction of transposition of great arteries (Gibbs *et al*). 67
- in bioprosthetic valve assessment, comparison of valves (Simpson *et al*). 83
- non-invasive estimation of mean pressure difference in aortic stenosis (Teien *et al*). 450
- pulsed, non-invasive estimates of pulmonary hypertension, reliability (Matsuda *et al*). 158
- and cross sectional echocardiography, in coronary heart disease in neonates (Leung *et al*). 73
- Double inlet left ventricle, staged septation: case report (McKay *et al*). 563
- Double outlet right ventricle and complete transposition, anatomical correction, intermediate assessment of functional results (Lincoln *et al*). 259
- Echocardiography
- cross sectional, in assessment of surgical "mitral valve" disease, children and adolescents (Ortiz & Somerville). 267
- right ventricle, normal adult (Foale *et al*). 33
- serial, in evaluation of viral myocarditis simulating dilated cardiomyopathy (Weinhouse *et al*). 94
- Editorials
- Congenital heart disease in adults and adolescents (Somerville). 395
- Early treatment of unstable angina (Fox & Krikler). 398
- Familial hypercholesterolaemia as an example of early diagnosis of coronary artery disease risk by DNA techniques (Humphries). 201
- Interventional catheterisation in infants and children (Bull). 197
- Is atrial natriuretic peptide really a hormone (Linden & Knapp). 299
- The pulse in atrial fibrillation (Meijler). 1
- Twenty years of prehospital coronary care (Geddes). 491
- Enalapril and frusemide combined, in congestive heart failure, reversible renal failure after: correspondence (Stewart *et al*: McMurray & Matthews: Funck-Brentano *et al*). 489
- Endomyocardial biopsy
- in life-threatening arrhythmias with unexpected myocardial disease (Hosenpud *et al*). 55
- peripartum heart disease (Sanderson *et al*). 285
- fibrosis, unusual echocardiographic appearance of intracardiac thrombi: case report (Wiseman *et al*). 179
- Epoprostenol sodium (prostacyclin) infusion, in acute myocardial infarction (Kiernan *et al*). 428
- Ergometrine maleate, effect on incidence of spasm at site of previous successful transluminal coronary angioplasty (Quyyumi *et al*). 27
- Eustachian valve, infective endocarditis affecting: case report (Edwards *et al*). 561
- Exercise
- capacity and spontaneous heart rhythm, after transvenous fulguration of atrioventricular conduction (Schofield *et al*). 358
- digital subtraction ventriculography, for detection of ischaemic wall motion abnormalities without myocardial infarction (Detrano *et al*). 131
- testing, in myocardial ischaemia, haemodynamic response to pulmonary artery pressure monitoring (Levy *et al*). 12
- tolerance in chronic heart block, ventricular pacing improving (Papouchado & Pitcher). 366
- Fibrillation, atrial
- pulse in: editorial (Meijler). 1
- pulse in, irregularly irregular (Rawles & Rowland). 4
- Frusemide and enalapril combined, in congestive heart failure, reversible renal failure after: correspondence (Stewart *et al*: McMurray & Matthews: Funck-Brentano *et al*). 489
- Global myocardial metabolism, influence of glyceryl trinitrate and nifedipine, during coronary artery operation (van Wezel *et al*). 272
- Glyceryl trinitrate and nifedipine, influence on coronary sinus blood flow and global myocardial metabolism during coronary artery operation (van Wezel *et al*). 272
- Heart
- block, chronic, ventricular pacing improves exercise tolerance (Papouchado & Pitcher). 366
- complete, with myocardial abscess, complicating anaerobic infective endocarditis: case report (Kopelman *et al*). 101
- fatal, due to mesothelioma of atrioventricular node: case report (Evans & Stovin). 572
- pathogenesis, in fatal case of dermatomyositis. case report (Behan *et al*). 479
- disease, peripartum, endomyocardial biopsy study (Sanderson *et al*). 285
- severe congestive, effects of captopril and hydralazine and iso-

- sorbide dinitrate on myocardial sympathetic tone (Daly *et al.*) 152
- Hearts, conjoined. case report (Antonelli *et al.*) 486
- Hunter, John, on heart disease: review (Proudfit). 109
- Hydralazine and isosorbide dinitrate, and captopril, effects on myocardial sympathetic tone in severe congestive heart failure (Daly *et al.*) 152
- Hypercholesterolaemia, familial, as example of early diagnosis of coronary artery disease risk by DNA techniques: editorial (Humphries) 201
- Hypertrophic cardiomyopathy
- effects of verapamil (Wilmschurst *et al.*) 544
 - without asymmetrical septal hypertrophy, pathological features: case report (Tanaka *et al.*) 294
- Infarct artery patency, initial ST segment elevation and final infarct size (Hackworthy *et al.*) 222
- Infective endocarditis
- affecting eustachian valve: case report (Edwards *et al.*) 561
 - anaerobic, myocardial abscess with complete heart block complicating (Kopelman *et al.*) 101
- Intracoronary thrombolytic treatment case report (Singh & Rutley). 182
- Ischaemic wall motion abnormalities without myocardial infarction, exercise digital subtraction ventriculography for detection (Detrano *et al.*) 131
- Lipoproteins and serum apolipoproteins AI and B, and ischaemic heart disease (Durrington *et al.*) 206
- M mode echocardiographic long axis and short axis left ventricular function derivatives, comparability (D'Arbela *et al.*) 445
- Magnetic resonance assessment
- of aortic and mitral regurgitation (Underwood *et al.*) 455
 - in assessment of regional left ventricular function (Underwood *et al.*) 334
- Mammary artery graft, internal, stenosis, transluminal angioplasty: case report (Crean *et al.*) 473
- Mesothelioma of atrioventricular node, causing fatal heart block: case report (Evans & Stovin) 572
- Metoprolol, in unstable angina, HINT Research Group. 400
- Monitoring *see* Pulmonary artery pressure monitoring
- Mitral
- regurgitation, magnetic resonance assessment (Underwood *et al.*) 455
 - valve, anomalous, causing left ventricular outflow tract obstruction, successful replacement, four month old infant: case report (Morais *et al.*) 385
 - disease, surgical, assessment by cross sectional echocardiography, children and adolescents (Ortiz & Somerville). 267
- Myocardial
- abscess with 'complete heart block', complicating anaerobic infective endocarditis: case report (Kopelman *et al.*) 101
 - infarction, coincidence of true and false left ventricular aneurysms after: case report (Coupe *et al.*) 567
 - constrictive pericarditis after: case report (Ramsdale *et al.*) 476
 - epoprostenol sodium (prostacyclin) infusion (Kiernan *et al.*) 428
 - impending, changes in left ventricular regional asynchrony after intracoronary thrombolysis (Gibson *et al.*) 121
 - infarct artery patency, initial ST segment elevation and final infarct size (Hackworthy *et al.*) 222
 - intracoronary, streptokinase, long-term improvement, global left ventricular function (Res *et al.*) 414
 - thrombolytic treatment: case report (Singh & Rutley) 182
 - and serum apolipoproteins AI and B and lipoproteins (Durrington *et al.*) 206
 - streptokinase treatment, crescentic glomerulonephritis as possible complication. case report (Murray *et al.*) 483
 - survival of non-surgical patients (Proudfit *et al.*) 213
 - in systemic lupus erythematosus, deep vein thrombosis, and antibodies to phospholipid: case report (Asherson *et al.*) 190
 - wall motion score, cross sectional echocardiography (Kan *et al.*) 422
 - ischaemia with variant angina, ambulatory pulmonary artery pressure monitoring (Levy *et al.*) 518
- Myxoma
- left atrial, new perspectives in diagnosis of murmur free cases (Nihoyannopoulos *et al.*) 554
 - right atrial, prolapsing, causing abnormal diastolic movement of interventricular septum case report (Ramsdale *et al.*) 569
- Nifedipine
- influence on coronary sinus blood flow and global myocardial metabolism during coronary artery operation (van Wezel *et al.*) 272
 - in unstable angina, HINT Research Group 400
- Notices 576
- Osteogenesis imperfecta, left atrial rupture: case report (Rogerson *et al.*) 187
- Pacemaker, QuinTech Tx, failure, caused by loss of stimulus-T interval shortening during exercise: case report (Fyfe & Robinson) 391
- Pacing
- mode, optimum, in angina pectoris (Kenney *et al.*) 463
 - ventricular, improves exercise tolerance in chronic heart block (Papouchado & Pitcher). 366
- Palmoplantar keratosis, familial, cardiac abnormalities (Protonotarios *et al.*) 321
- Percutaneous transluminal coronary angioplasty
- coronary artery thrombus as risk factor (Sugrue *et al.*) 62
 - early results, 400 patients (Sowton *et al.*) 115
 - incidence of spasm at site, effect of ergometrine maleate (Quyyumi *et al.*) 27
 - influence of variant angina on results (Leisch *et al.*) 341
 - of occluded left anterior descending coronary artery: case report (Grollier *et al.*) 377
 - of stenosis of internal mammary artery graft case report (Crean *et al.*) 473
- Pericarditis, constrictive, after myocardial infarction. case report (Ramsdale *et al.*) 476
- Prostheses, Doppler ultrasound assessment, comparison of valves (Simpson *et al.*) 83
- Peripartum heart disease, endomyocardial biopsy study (Sanderson *et al.*) 285
- Proteins, contractile, postoperative immunological response against, after coronary bypass surgery (de Scheerder *et al.*) 440
- Pulmonary
- artery pressure monitoring assessment of haemodynamic response in myocardial ischaemia (Levy *et al.*) 12
 - right, anomalous origin from aorta, surgical correction, four day old neonate: case report (Sibley *et al.*) 98
 - hypertension, non-invasive estimates by pulsed Doppler echocardiography, reliability (Matsuda *et al.*) 158
 - hypertensive duct and aortic valve stenosis, successful balloon aortic valvotomy case report (Rickards & Somerville). 185
 - stenosis, balloon dilatation (Rao) 250
- Pulse
- in atrial fibrillation: editorial (Meijler). 1
 - irregularly irregular (Rawles & Rowland). 4
- QuinTech Tx pacemaker, failure, caused by loss of stimulus-T interval shortening during exercise. case report (Fyfe & Robinson) 391
- Radiation hazards for cardiologists: correspondence (Wilde). 394

- Renal failure, reversible, after combined enalapril and frusemide, in coronary heart failure: correspondence (Stewart *et al.*; McMurray & Matthews; Fock-Brentano *et al.*). 489
- Sarcoid heart disease in patients with life threatening arrhythmias: correspondence (Fleming). 575
- Septation, staged, double inlet left ventricle. case report (McKay *et al.*). 563
- Sinoatrial disease, oral xamoterol in (Tseu *et al.*). 469
- Smoking, major predictor of left ventricular function after occlusion of left anterior descending coronary artery (McKenzie *et al.*). 496
- Sodium nitroprusside and trimetaphan camsylate compared for effects on plasma catecholamine changes during cardiopulmonary bypass (Corr *et al.*). 89
- Somatostatin, electrophysiological actions on atrioventricular junction, in sinus rhythms and reentry tachycardia (Webb *et al.*). 236
- Spasm, incidence at site of previous successful transluminal coronary angioplasty, effect of ergometrine maleate (Quyumi *et al.*). 27
- Spontaneous heart rhythm and exercise capacity, after transvenous fulguration of atrioventricular conduction (Schofield *et al.*). 358
- ST segment
in ambulatory pulmonary artery pressure monitoring, in myocardial ischaemia with variant angina (Levy *et al.*). 518
depression, asymptomatic, assessed by ambulatory pulmonary artery pressure monitoring, haemodynamic significance (Levy *et al.*). 526
haemodynamic significance, and syndrome X (Levy *et al.*). 353
elevation and final infarct size, influence of infarct artery patency (Hackworthy *et al.*). 222
- Streptokinase
intracoronary, in myocardial infarction, long-term improvement, global left ventricular function (Res *et al.*). 414
treatment for myocardial infarction, crescentic glomerulonephritis as possible complication: case report (Murray *et al.*). 483
- Sweating, profuse, influence on systolic time intervals (Ishikawa & Ishikawa). 176
- Syndrome X, haemodynamic significance of ST segment depression (Levy *et al.*). 353
- Systemic lupus erythematosus, deep vein thrombosis, and antibodies to phospholipid, and myocardial infarction: case report (Asherson *et al.*). 190
- Systolic time intervals, influence of profuse sweating (Ishikawa & Ishikawa). 176
- Tachycardia, ventricular, of right ventricular origin, right ventricular abnormalities, relation to electrophysiological abnormalities (Foale *et al.*). 45
- Thallium scintigraphy, detecting coronary artery disease in valvar heart disease (Huikuri *et al.*). 146
- Thrombi, intracardiac, in endomyocardial fibrosis, unusual echocardiographic appearance: case report (Wiseman *et al.*). 179
- Thrombolysis, intracoronary, treatment: case report (Singh & Ruttley). 182
in impending myocardial infarction, changes in left ventricular regional asynchrony after (Gibson *et al.*). 121
- Thromboxane receptor blocking drug AH23848, effect in angina pectoris (De Bono *et al.*). 509
- Transposition of the great arteries
anatomical correction, Doppler echocardiography after (Gibbs *et al.*). 67
complete, and double outlet right ventricle, anatomical correction, intermediate assessment of functional results (Lincoln *et al.*). 259
- Transvenous fulguration of atrioventricular conduction, exercise capacity and spontaneous heart rhythm after (Schofield *et al.*). 358
- Trefoil balloon, for aortic valvuloplasty: case report (Meier *et al.*). 292
- Tricuspid atresia, in adolescents and adults, current state and late complications (Warnes & Somerville). 535
- Trimetaphan camsylate and sodium nitroprusside compared for effects on plasma catecholamine changes during cardiopulmonary bypass (Corr *et al.*). 89
- Truncus arteriosus, successful surgical correction without use of valved conduit: case report (Reid *et al.*). 388
- Validation of study 576
- Valvar heart disease, detection of coronary artery disease by thallium scintigraphy (Huikuri *et al.*). 146
- Valvotomy, balloon aortic, successful, in pulmonary hypertensive duct and aortic stenosis: case report (Rickards & Somerville). 185
- Valvuloplasty, aortic, trefoil balloon. case report (Meier *et al.*). 292
- Variant angina *see* Angina pectoris, variant
- Vasopressin antagonist, in congestive heart failure, hormonal, global, and regional haemodynamic responses (Nicod *et al.*). 433
- Ventricles, left
aneurysms, true and false, after myocardial infarction, coincidence: case report (Coupe *et al.*). 567
dysfunction in angina pectoris and normal coronary angiograms (Schofield *et al.*). 327
function after occlusion of left anterior descending coronary artery, smoking as major predictor (McKenzie *et al.*). 496
derivatives, comparability of M mode echocardiographic long axis and short axis (D'Arbela *et al.*). 445
regional, assessment by magnetic resonance (Underwood *et al.*). 334
hypertrophy, electrocardiographic and echocardiographic measures compared, in assessment of aortic stenosis. correspondence (Bennett; Wainwright Evans & Raj; Dancy). 105
outflow tract obstruction, due to anomalous mitral valve, successful replacement, four month old infant: case report (Morais *et al.*). 385
regional asynchrony, changes, after intracoronary thrombolysis in impending myocardial infarction (Gibson *et al.*). 121
wall motion, regional variation in timing and extent, normal subjects (Hammermeister *et al.*). 226
- Ventricles, right
abnormalities, in ventricular tachycardia of right ventricular origin, relation to electrophysiological abnormalities (Foale *et al.*). 45
infarction, diagnosis and prognosis (Rodrigues *et al.*). 19
normal adult, echocardiographic measurement (Foale *et al.*). 33
- Ventricular
septal defect, evaluation of aortic valve prolapse (Menahem *et al.*). 242
tachycardia and α receptors, after clonidine withdrawal correspondence (Nakagawa *et al.*). 194
of right ventricular origin, right ventricular abnormalities, relation to electrophysiological abnormalities (Foale *et al.*). 45
- Verapamil, effects, in hypertrophic cardiomyopathy (Wilmshurst *et al.*). 544
- Viral myocarditis simulating dilated cardiomyopathy, in early childhood, evaluation by serial echocardiography (Weinhouse *et al.*). 94
- Xamoterol, oral, in sinoatrial disease (Tseu *et al.*). 469

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CONTENTS OF VOLUME 56

Number 1

EDITORIAL: THE PULSE IN ATRIAL FIBRILLATION	F L Meijler	1
IS THE PULSE IN ATRIAL FIBRILLATION IRREGULARLY IRREGULAR?	J M Rawles, E Rowland	4
HAEMODYNAMIC RESPONSE TO MYOCARDIAL ISCHAEMIA DURING UNRESTRICTED ACTIVITY, EXERCISE TESTING, AND ATRIAL PACING ASSESSED BY AMBULATORY PULMONARY ARTERY PRESSURE MONITORING	R D Levy, L M Shapiro, C Wright, L Mockus, K M Fox	12
DIAGNOSIS AND PROGNOSIS OF RIGHT VENTRICULAR INFARCTION	E A Rodrigues, N G Dewhurst, L M Smart, W J Hannan, A L Muir	19
INCIDENCE OF SPASM AT THE SITE OF PREVIOUS SUCCESSFUL TRANSLUMINAL CORONARY ANGIOPLASTY: EFFECT OF ERGOMETRINE MALEATE IN CONSECUTIVE PATIENTS	A A Quyyumi, M Raphael, E J Perrins, L M Shapiro, A F Rickards, K M Fox	27
ECHOCARDIOGRAPHIC MEASUREMENT OF THE NORMAL ADULT RIGHT VENTRICLE	R Foale, P Nihoyannopoulos, W McKenna, A Kleinebenne, A Nadazdin, E Rowland, G Smith	33
RIGHT VENTRICULAR ABNORMALITIES IN VENTRICULAR TACHYCARDIA OF RIGHT VENTRICULAR ORIGIN: RELATION TO ELECTROPHYSIOLOGICAL ABNORMALITIES	R A Foale, P Nihoyannopoulos, P Ribeiro, W J McKenna, C M Oakley, D M Krikler, E Rowland	45
UNEXPECTED MYOCARDIAL DISEASE IN PATIENTS WITH LIFE THREATENING ARRHYTHMIAS	J D Hosenpud, J H McAnulty, N R Niles	55
CORONARY ARTERY THROMBUS AS A RISK FACTOR FOR ACUTE VESSEL OCCLUSION DURING PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY. IMPROVING RESULTS	D D Sugrue, D R Holmes Jr, H C Smith, G S Reeder, G E Lane, R E Vlietstra, J F Bresnahan, L N Hammes, J M Piehler	62
DOPPLER ECHOCARDIOGRAPHY AFTER ANATOMICAL CORRECTION OF TRANSPOSITION OF THE GREAT ARTERIES	J L Gibbs, S A Qureshi, L Grieve, C Webb, R Radley Smith, M H Yacoub	67
THE ROLE OF CROSS SECTIONAL ECHOCARDIOGRAPHY AND PULSED DOPPLER ULTRASOUND IN THE MANAGEMENT OF NEONATES IN WHOM CONGENITAL HEART DISEASE IS SUSPECTED: A PROSPECTIVE STUDY	M P Leung, C K Mok, K C Lau, R Lo, C Y Yeung	73
NON-INVASIVE ASSESSMENT BY DOPPLER ULTRASOUND OF 155 PATIENTS WITH BIOPROSTHETIC VALVES: A COMPARISON OF THE WESSEX PORCINE, LOW PROFILE IONESCU-SHILEY, AND HANCOCK PERICARDIAL BIOPROSTHESES	I A Simpson, I J Reece, A B Houston, I Hutton, D J Wheatley, S M Cobbe	83
PLASMA CATECHOLAMINE CHANGES DURING CARDIOPULMONARY BYPASS: A RANDOMISED DOUBLE BLIND COMPARISON OF TRIMETAPHAN CAMSYLATE AND SODIUM NITROPRUSSIDE	L Corr, R M Grounds, M J Brown, J G Whitwam	89
VIRAL MYOCARDITIS SIMULATING DILATED CARDIOMYOPATHY IN EARLY CHILDHOOD: EVALUATION BY SERIAL ECHOCARDIOGRAPHY	E Weinhouse, K L Wanderman, S Sofer, Y Gussarsky, M Gueron	94
CASE REPORTS		
SURGICAL CORRECTION OF ANOMALOUS ORIGIN OF RIGHT PULMONARY ARTERY FROM AORTA IN A FOUR DAY OLD NEONATE	Y D L Sibley, K D Roberts, E D Silove	98
MYOCARDIAL ABSCESS WITH COMPLETE HEART BLOCK COMPLICATING ANAEROBIC INFECTIVE ENDOCARDITIS	H A Kopelman, B S Graham, M B Forman	101
CORRESPONDENCE		105
NOTICE		108

Number 2

REVIEW: JOHN HUNTER. ON HEART DISEASE	W L Proudfit	109
EARLY RESULTS AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY IN 400 PATIENTS E Sowton, A D Timmis, J C P Crick, B Griffin, A K Yates, P Deverall		115
CHANGES IN LEFT VENTRICULAR REGIONAL ASYNCHRONY AFTER INTRACORONARY THROMBOLYSIS IN PATIENTS WITH IMPENDING MYOCARDIAL INFARCTION D Gibson, H Mehmehl, F Schwarz, K Li, W Kübler		121
EXERCISE DIGITAL SUBTRACTION VENTRICULOGRAPHY FOR THE DETECTION OF ISCHAEMIC WALL MOTION ABNORMALITIES IN PATIENTS WITHOUT MYOCARDIAL INFARCTION R Detrano, J Yiannikas, C Simpfendorfer, R E Hobbs, E E Salcedo		131
DIAGNOSIS OF IMPORTANT FIXED CORONARY STENOSIS IN PATIENTS WITH VARIANT ANGINA BY EXERCISE TESTS AFTER TREATMENT WITH CALCIUM ANTAGONISTS H Araki, N Hayata, T Matsuguchi, A Takeshita, M Nakamura		138
DETECTION OF CORONARY ARTERY DISEASE BY THALLIUM SCINTIGRAPHY IN PATIENTS WITH VALVAR HEART DISEASE H V Huikuri, U R Korhonen, J Heikkilä, J T Takkanen		146
EFFECTS OF CAPTOPRIL AND A COMBINATION OF HYDRALAZINE AND ISOSORBIDE DINITRATE ON MYOCARDIAL SYMPATHETIC TONE IN PATIENTS WITH SEVERE CONGESTIVE HEART FAILURE P Daly, J-L Rouleau, D Cousineau, J H Burgess, K Chatterjee		152
RELIABILITY OF NON-INVASIVE ESTIMATES OF PULMONARY HYPERTENSION BY PULSED DOPPLER ECHOCARDIOGRAPHY M Matsuda, T Sekiguchi, Y Sugishita, K Kuwako, K Iida, I Ito		158
RELATION BETWEEN ALCOHOL INTAKE, MYOCARDIAL ENZYME ACTIVITY, AND MYOCARDIAL FUNCTION IN DILATED CARDIOMYOPATHY: EVIDENCE FOR THE CONCEPT OF ALCOHOL INDUCED HEART MUSCLE DISEASE P J Richardson, A D Wodak, L Atkinson, J B Saunders, D E Jewitt		165
COMPUTED TOMOGRAPHY: THE INVESTIGATION OF CHOICE FOR AORTIC DISSECTION? H Singh, E Fitzgerald, M S T Ruttlely		171
INFLUENCE OF PROFUSE SWEATING ON SYSTOLIC TIME INTERVALS M Ishikawa, K Ishikawa		176
CASE REPORTS		
UNUSUAL ECHOCARDIOGRAPHIC APPEARANCE OF INTRACARDIAC THROMBI IN A PATIENT WITH ENDOMYOCARDIAL FIBROSIS M N Wiseman, M S Giles, A J Camm		179
INTRACORONARY THROMBOLYTIC TREATMENT. ANOTHER HAZARD H Singh, M S T Ruttlely		182
SUCCESSFUL BALLOON AORTIC VALVOTOMY IN A CHILD WITH A PULMONARY HYPERTENSIVE DUCT AND AORTIC VALVE STENOSIS A F Rickards, J Somerville		185
LEFT ATRIAL RUPTURE IN OSTEOGENESIS IMPERFECTA M E Rogerson, J D Buchanan, C M Morgans		187
MYOCARDIAL INFARCTION IN A YOUNG MAN WITH SYSTEMIC LUPUS ERYTHEMATOSUS, DEEP VEIN THROMBOSIS, AND ANTIBODIES TO PHOSPHOLIPID R A Asherson, I R Mackay, E N Harris		190
NOTICES		193
CORRESPONDENCE		194

Number 3

EDITORIAL INTERVENTIONAL CATHETERISATION IN INFANTS AND CHILDREN	C Bull	197
EDITORIAL: FAMILIAL HYPERCHOLESTEROLAEMIA AS AN EXAMPLE OF EARLY DIAGNOSIS OF CORONARY ARTERY DISEASE RISK BY DNA TECHNIQUES	S E Humphries	201
SERUM APOLIPOPROTEINS AI AND B AND LIPOPROTEINS IN MIDDLE AGED MEN WITH AND WITHOUT PREVIOUS MYOCARDIAL INFARCTION	P N Durrington, L Hunt, M Ishola, J Kane, W P Stephens	206
SURVIVAL OF NON-SURGICAL PATIENTS WITH MILD ANGINA OR MYOCARDIAL INFARCTION WITHOUT ANGINA	W L Proudfit, J R Kramer, C Bott-Silverman, M Goormastic	213
INFLUENCE OF INFARCT ARTERY PATENCY ON THE RELATION BETWEEN INITIAL ST SEGMENT ELEVATION AND FINAL INFARCT SIZE	R A Hackworthy, M B Vogel, P J Harris	222
REGIONAL VARIATION IN THE TIMING AND EXTENT OF LEFT VENTRICULAR WALL MOTION IN NORMAL SUBJECTS	K E Hammermeister, D G Gibson, D Hughes, and Participants in Veterans Administration Cooperative Study on Valvular Heart Disease	226
ELECTROPHYSIOLOGICAL ACTIONS OF SOMATOSTATIN ON THE ATRIOVENTRICULAR JUNCTION IN SINUS RHYTHM AND REENTRY TACHYCARDIA	S C Webb, D M Krikler, W G Hendry, T E Adrian, S R Bloom	236
EVALUATION OF AORTIC VALVE PROLAPSE IN VENTRICULAR SEPTAL DEFECT	S Menahem, J A Johns, S del Torso, T H Goh, A W Venables	242
TRANSCATHETER TREATMENT OF PULMONARY STENOSIS AND COARCTATION OF THE AORTA: EXPERIENCE WITH PERCUTANEOUS BALLOON DILATATION	P S Rao	250
ANATOMICAL CORRECTION FOR COMPLETE TRANSPOSITION AND DOUBLE OUTLET RIGHT VENTRICLE: INTERMEDIATE ASSESSMENT OF FUNCTIONAL RESULTS	C Lincoln, A-N-Redington, K Li, S Mattos, E A Shinebourne, M L Rigby	259
ASSESSMENT BY CROSS SECTIONAL ECHOCARDIOGRAPHY OF SURGICAL "MITRAL VALVE" DISEASE IN CHILDREN AND ADOLESCENTS	E Ortiz, J Somerville	267
INFLUENCE OF GLYCERYL TRINITRATE AND NIFEDIPINE ON CORONARY SINUS BLOOD FLOW AND GLOBAL MYOCARDIAL METABOLISM DURING CORONARY ARTERY OPERATION	H B van Wezel, J G Bovill, J J Koolen, M R Patrick, J W T Fiolet, J G van der Stroom	272
INTRAVENOUS AND ORAL AMIODARONE FOR ARRHYTHMIAS IN CHILDREN	C A Bucknall, B R Keeton, P V L Curry, M J Tynan, G R Sutherland, D W Holt	278
PERIPARTUM HEART DISEASE: AN ENDOMYOCARDIAL BIOPSY STUDY	J E Sanderson, E G J Olsen, D Gatei	285
CASE REPORTS		
TREFOIL BALLOON FOR AORTIC VALVULOPLASTY	B Meier, B Friedli, I Oberh�nsli	292
PATHOLOGICAL FEATURES OF HYPERTROPHIC CARDIOMYOPATHY WITHOUT ASYMMETRICAL SEPTAL HYPERTROPHY	M Tanaka, H Fujiwara, C Kawai	294
NOTICES		298
CORRECTION. ECHOCARDIOGRAPHIC MEASUREMENT OF THE NORMAL ADULT RIGHT VENTRICLE	R Foale, P Nihoyannopoulos, W McKenna, A Kleinbenne, A Nadazdin, E Rowland, G Smith	298



Number 4

EDITORIAL: IS ATRIAL NATRIURETIC PEPTIDE REALLY A HORMONE?	R J Linden, M F Knapp	299
THE ATRIAL NATRIURETIC FACTOR	J Genest	302
ISOLATED ATRIAL AMYLOID CONTAINS ATRIAL NATRIURETIC PEPTIDE: A REPORT OF SIX CASES	G C Kaye, M G Butler, A J d'Ardenne, S J Edmondson, A J Camm, G Slavin	317
CARDIAC ABNORMALITIES IN FAMILIAL PALMOPLANTAR KERATOSIS	N Protonotarios, A Tsatsopoulou, P Patsourakos, D Alexopoulos, P Gezerlis, S Simitsis, G Scampardonis	321
LEFT VENTRICULAR DYSFUNCTION IN PATIENTS WITH ANGINA PECTORIS AND NORMAL CORONARY ANGIOGRAMS	P M Schofield, N H Brooks, D H Bennett	327
ASSESSMENT OF REGIONAL LEFT VENTRICULAR FUNCTION BY MAGNETIC RESONANCE	S R Underwood, R S O Rees, P E Savage, R H Klipstein, D N Firmin, K M Fox, P A Poole-Wilson, D B Longmore	334
INFLUENCE OF A VARIANT ANGINA ON THE RESULTS OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY	F Leisch, W Schützenberger, K Kerschner, W Herbinger	341
NOCTURNAL ANGINA: PRECIPITATING FACTORS IN PATIENTS WITH CORONARY ARTERY DISEASE AND THOSE WITH VARIANT ANGINA	A A Quyyumi, J Efthimiou, A Quyyumi, L J Mockus, S G Spiro, K M Fox	346
SYNDROME X THE HAEMODYNAMIC SIGNIFICANCE OF ST SEGMENT DEPRESSION	R D Levy, L M Shapiro, C Wright, L Mockus, K M Fox	353
EXERCISE CAPACITY AND SPONTANEOUS HEART RHYTHM AFTER TRANSVENOUS ABLATION OF ATRIOVENTRICULAR CONDUCTION	P M Schofield, R J Bowes, N Brooks, D H Bennett	358
VENTRICULAR PACING IMPROVES EXERCISE TOLERANCE IN PATIENTS WITH CHRONIC HEART BLOCK	M Papouchado, D W Pitcher	366
VALUE OF THE BIPOLAR LEAD CM5 IN ELECTROCARDIOGRAPHY	A A Quyyumi, T Crake, L J Mockus, C A Wright, A F Rickards, K M Fox	372
CASE REPORTS		
ANGIOPLASTY OF AN OCCLUDED LEFT ANTERIOR DESCENDING CORONARY ARTERY. USEFULNESS OF RETROGRADE OPACIFICATION OF THE DISTAL PART OF THE OCCLUDED VESSEL VIA THE CONTRALATERAL CORONARY ARTERY IN POSITIONING THE BALLOON CATHETER	G Grollier, Ph Commeau, J C Potier	377
CONGENITAL DIVERTICULUM OF THE HEART ARISING FROM THE CORONARY SINUS	E Di Segni, A Siegal, M Katzenstein	380
LEFT VENTRICULAR OUTFLOW TRACT OBSTRUCTION DUE TO ANOMALOUS MITRAL VALVE: SUCCESSFUL MITRAL VALVE REPLACEMENT IN A FOUR MONTH OLD INFANT	P Morais, S Westaby, K A Hallidie-Smith	385
TRUNCUS ARTERIOSUS: SUCCESSFUL SURGICAL CORRECTION WITHOUT THE USE OF A VALVED CONDUIT	K G Reid, M J Godman, J E Burns	388
FAILURE OF QUINTECH TX PACEMAKER CAUSED BY LOSS OF STIMULUS-T INTERVAL SHORTENING DURING EXERCISE	T Fyfe, J F Robinson	391
CORRESPONDENCE		394
NOTICES		394

Number 5

EDITORIAL. CONGENITAL HEART DISEASE IN ADULTS AND ADOLESCENTS	J Somerville	395
EDITORIAL. EARLY TREATMENT OF UNSTABLE ANGINA	K M Fox, D M Krikler	398
EARLY TREATMENT OF UNSTABLE ANGINA IN THE CORONARY CARE UNIT: A RANDOMISED, DOUBLE BLIND, PLACEBO CONTROLLED COMPARISON OF RECURRENT ISCHAEMIA IN PATIENTS TREATED WITH NIFEDIPINE OR METOPROLOL OR BOTH	<i>The Holland Interuniversity Nifedipine/metoprolol Trial (HINT) research group</i>	400
LONG TERM IMPROVEMENT IN GLOBAL LEFT VENTRICULAR FUNCTION AFTER EARLY THROMBOLYTIC TREATMENT IN ACUTE MYOCARDIAL INFARCTION: REPORT OF A RANDOMISED MULTICENTRE TRIAL OF INTRACORONARY STREPTOKINASE IN ACUTE MYOCARDIAL INFARCTION	J C J Res, M L Simoons, E E van der Wall, M J van Eenige, F Vermeer, F W A Verheugt, W Wijns, S Braat, W J Remme, P W Serruys, J P Roos	414
SHORT AND LONG TERM PREDICTIVE VALUE OF ADMISSION WALL MOTION SCORE IN ACUTE MYOCARDIAL INFARCTION: A CROSS SECTIONAL ECHOCARDIOGRAPHIC STUDY OF 345 PATIENTS	G Kan, C A Visser, J J Koolen, A J Dunning	422
EPOPROSTENOL SODIUM (PROSTACYCLIN) INFUSION IN ACUTE MYOCARDIAL INFARCTION	F J Kiernan, J Kluger, J C Regnier, M Rutkowski, A Fieldman	428
HORMONAL, GLOBAL, AND REGIONAL HAEMODYNAMIC RESPONSES TO A VASCULAR ANTAGONIST OF VASOPRESSIN IN PATIENTS WITH CONGESTIVE HEART FAILURE WITH AND WITHOUT HYPONATRAEMIA	P Nicod, J Biollaz, B Waeber, J J Goy, R Polikar, J Schlapfer, M D Schaller, G A Turini, J Nussberger, K G Hofbauer, H R Brunner	433
POSTOPERATIVE IMMUNOLOGICAL RESPONSE AGAINST CONTRACTILE PROTEINS AFTER CORONARY BYPASS SURGERY	I De Scheerder, M De Buyzere, J Robbrecht, M De Lange, J Delanghe, A M Bogaert, D Clement	440
COMPARABILITY OF M MODE ECHOCARDIOGRAPHIC LONG AXIS AND SHORT AXIS LEFT VENTRICULAR FUNCTION DERIVATIVES	P G D'Arbela, Z M Silayan, J M Bland	445
NON-INVASIVE ESTIMATION OF THE MEAN PRESSURE DIFFERENCE IN AORTIC STENOSIS BY DOPPLER ULTRASOUND	D Teien, K Karp, P Eriksson	450
MAGNETIC RESONANCE ASSESSMENT OF AORTIC AND MITRAL REGURGITATION	S R Underwood, R H Klipstein, D N Firmin, K M Fox, P A Poole-Wilson, R S O Rees, D B Longmore	455
OPTIMUM PACING MODE FOR PATIENTS WITH ANGINA PECTORIS	R A Kenny, A Ingram, T Mitsuoka, K Walsh, R Sutton	463
ORAL XAMOTEROL IN PATIENTS WITH SINOATRIAL DISEASE	F L Tseu, C A Morley, A F Mackintosh	469
CASE REPORTS		
TRANSLUMINAL ANGIOPLASTY OF A STENOSIS OF AN INTERNAL MAMMARY ARTERY GRAFT	P A Crean, P W Mathieson, A F Rickards	473
CONSTRICTIVE PERICARDITIS AFTER MYOCARDIAL INFARCTION	D R Ramsdale, E J Epstein, N Coulshed	476
PATHOGENESIS OF HEART BLOCK IN A FATAL CASE OF DERMATOMYOSITIS	W M H Behan, M Aitchison, P O Behan	479
CRESCENTIC GLOMERULONEPHRITIS: A POSSIBLE COMPLICATION OF STREPTOKINASE TREATMENT FOR MYOCARDIAL INFARCTION	N Murray, J Lyons, M Chappell	483
CONJOINED HEARTS	D Antonelli, L Shmilovitz, M Dharan	486
NOTICES		488
CORRESPONDENCE		489

Number 6

EDITORIAL TWENTY YEARS OF PREHOSPITAL CORONARY CARE	J S Geddes	491
SMOKING A MAJOR PREDICTOR OF LEFT VENTRICULAR FUNCTION AFTER OCCLUSION OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY	W B McKenzie, R M McCredie, C A McGilchrist, D E L Wilcken	496
MORPHOLOGICAL CHARACTERISTICS OF CLINICALLY SIGNIFICANT CORONARY ARTERY STENOSIS IN STABLE ANGINA	J R W Hangartner, A J Charleston, M J Davies, A C Thomas	501
EFFECT OF THE SPECIFIC THROMBOXANE RECEPTOR BLOCKING DRUG AH23848 IN PATIENTS WITH ANGINA PECTORIS	D P De Bono, P Lumley, M Been, R Keery, S E Ince, D F Woodings	509
THE HAEMODYNAMIC RESPONSE TO MYOCARDIAL ISCHAEMIA IN AMBULANT PATIENTS WITH VARIANT ANGINA	R D Levy, L M Shapiro, C Wright, L J Mockus, K M Fox	518
THE HAEMODYNAMIC SIGNIFICANCE OF ASYMPTOMATIC ST SEGMENT DEPRESSION ASSESSED BY AMBULATORY PULMONARY ARTERY PRESSURE MONITORING	R D Levy, L M Shapiro, C Wright, L J Mockus, K M Fox	526
MECHANISM OF THE DICROTIC PULSE	D Smith, E Craige	531
TRICUSPID ATRESIA IN ADOLESCENTS AND ADULTS: CURRENT STATE AND LATE COMPLICATIONS	C A Warnes, J Somerville	535
EFFECTS OF VERAPAMIL ON HAEMODYNAMIC FUNCTION AND MYOCARDIAL METABOLISM IN PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY	P T Wilmshurst, D S Thompson, S M Juul, B S Jenkins, M M Webb-Peploe	544
LEFT ATRIAL MYXOMA NEW PERSPECTIVES IN THE DIAGNOSIS OF MURMUR FREE CASES	P Nihoyannopoulos, P Venkatesan, J David, D Hackett, H Valentine, C M Oakley	554
CASE REPORTS		
INFECTIVE ENDOCARDITIS AFFECTING THE EUSTACHIAN VALVE	A D Edwards, M A Vickers, C J Morgan	561
STAGED SEPTATION OF DOUBLE INLET LEFT VENTRICLE	R McKay, R M Bini, J P Wright	563
COINCIDENCE OF TRUE AND FALSE LEFT VENTRICULAR ANEURYSMS AFTER MYOCARDIAL INFARCTION	M Coupe, M Dancy, J Pepper	567
ABNORMAL DIASTOLIC MOVEMENT OF THE INTERVENTRICULAR SEPTUM CAUSED BY A PROLAPSING RIGHT ATRIAL MYXOMA	D R Ramsdale, G J Green, R G Charles	569
FATAL HEART BLOCK DUE TO MESOTHELIOMA OF THE ATRIOVENTRICULAR NODE	D W Evans, P G I Stovin	572
CORRESPONDENCE		575
NOTICES		576
VALIDATION OF STUDY		576
INDEX		577

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September 1986, 144pp.,
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This Autumn saw the launch of the 'Save a Life Campaign', organised by the Royal Society of Medicine, aimed at educating the general public in the recognition of acute emergencies and the application of resuscitation techniques. Evidence that pre-hospital emergency care effectively reduces fatalities and that intervention by both trained laypeople and professionals is particularly successful in the situation of coronary attack, is now widespread.

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